



Aminoacyl-tRNA synthetases of the multi-tRNA synthetase complex and their role in tumorigenesis

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ABSTRACT

In mammalian cells, 20 aminoacyl-tRNA synthetases (AARS) catalyze the ligation of amino acids to their cognate tRNAs to generate aminoacylated-tRNAs. In higher eukaryotes, 9 of the 20 AARSs, along with 3 auxiliary proteins, join to form the cytoplasmic multi-tRNA synthetase complex (MSC). The complex is absent in prokaryotes, but evolutionary expansion of MSC constituents, primarily by addition of novel interacting domains, facilitates formation of subcomplexes that join to establish the holo-MSC. In some cases, environmental cues direct the release of constituents from the MSC which enables the execution of non-canonical, i.e., “moonlighting”, functions distinct from their essential activities in protein translation. These activities are generally beneficial, but can also be deleterious to the cell. Elucidation of the non-canonical activities of several AARSs residing in the MSC suggest they are potential therapeutic targets for cancer, as well as metabolic and neurologic diseases. Here, we describe the role of MSC-resident AARSs in cancer progression, and the factors that regulate their release from the MSC. Also, we highlight recent developments in therapeutic modalities that target MSC AARSs for cancer prevention and treatment.

Introduction

AARSs are essential enzymes that synthesize building blocks of protein synthesis by ligating amino acids to their cognate tRNAs to form aminoacylated-tRNAs – essential for decoding genetic information through protein translation [1–3]. There are 20 cytoplasmic AARSs – one for each amino acid. The sequence and structure of the catalytic and anticodon binding domains of AARSs are highly conserved from prokaryotes to eukaryotes, supporting their early appearance and critical function in all organisms. Eukaryotic AARSs uniquely harbor novel domains appended during evolution, and which exert non-canonical functions unrelated to translation, but important in multiple complex pathophysiological processes including inflammation, amino acid metabolism, tumorigenesis, and neurodegeneration, among others [4–9]. In humans and other mammals, nine of the cytoplasmic AARSs, in addition to three scaffolding proteins termed AARS-interacting multi-functional proteins 1–3 (AIMP1–3), form a large ~1.25 MDa MSC (Fig. 1a,b) [10]. Altered expression or mutation of multiple MSC-resident AARSs correlates with poor cancer prognosis; in contrast, the auxiliary AIMP proteins can exhibit anti-tumorigenic activities [11–13]. The precise physiological function of the MSC remains elusive,

however, a critical role in sequestration of constituents with deleterious activities in free form has been proposed [14–16]. Thus, besides expression level, cellular localization of AARSs following release from the MSC can contribute importantly to physiological and pathological function. In many cases, pathogenic mutations do not influence AARS catalytic function, but rather alter their cell localization, and possibly their non-canonical function involved in tumor promotion, thus improving their therapeutic suitability as loss-of-function targets [13, 17]. Specific mechanisms of stimulus-dependent release of constituents are not well understood; however, the recent elucidation of the 3D architecture of the MSC by cross-linking mass-spectrometry (XL-MS) reveals specific interaction domains between constituents, and thus can provide insights into specific sites and domains critical for release [18]. Here, we review our current understanding of the function of MSC AARSs, and their alternative forms in tumor progression and prevention, as well as current therapeutic modalities that target them. There is limited or no data on the relationship of QARS1, IARS1, and RARS1 to cancer, and these are not discussed in detail.

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MSC-associated AARs and AIMPs and their role in cancer progression

Glutamyl-prolyl-tRNA synthetase (EPRS1)

EPRS1 is an ~170 kDa, bifunctional tRNA synthetase with glutamyl-tRNA synthetase activity near the N-terminus and proline-tRNA synthetase activity at the C-terminus (Fig. 1a). The catalytic domains are fused with a linker harboring three helix-turn-helix WHEP domains [19]. The GST-like domain at the N-terminus regulates protein-protein interactions critical for its association with the MSC [20,21]. A methylation microarray analysis showed that elevated *EPRS1* mRNA expression in breast cancer patients is associated with an unfavorable clinical outcome [22]. Likewise, *EPRS1* mRNA copy number is associated with increased tamoxifen-resistance and poor prognosis in ER⁺ breast cancer cells where it induces estrogen receptor expression and activity [23]. In an alternative mechanism, EPRS1 interaction with several extra-MSC proteins can contribute to cancer progression. For example, EPRS1 interacts with Engrailed1, a homeodomain transcription factor, and disruption of the interaction with synthetic peptides enhances tumor cell apoptosis [24]. In non-small-cell lung cancer (NSCLC) cells, DUS2 interaction with EPRS drives cell proliferation, presumably by enhancing tRNA charging activity [25]. In gastric cancer, over-expression of EPRS1 induces interaction with SYCL2, in turn activating the WNT/GSK-3 β / β -catenin signaling pathway, driving cell proliferation and tumor growth [26]. IFN- γ -treatment of macrophages, induces EPRS1 phosphorylation and release from the MSC to form the quaternary interferon- γ -activated inhibitor of translation (GAIT) complex with NSAP1, ribosomal protein L13a and GAPDH [27,28]. The complex silences translation of multiple inflammation-related transcripts, including vascular endothelial growth factor-A, an angiogenic

factor critical for growth of breast tumors, among others [29–31]. EPRS1 exhibits a non-canonical function as a terminal effector of the mTORC1-S6K1 axis determining adiposity, and mice bearing an EPRS1 Ser999-to-Ala-loss-of-function mutation are lean. In view of the role of obesity as a determinant of progression of certain cancer types, e.g., breast and ovarian cancer, it will be interesting to test the lean, mutant EPRS1 mice are resistant to these cancers.

Methionyl-tRNA synthetase (MARS1)

MARS1 is an ~100 kDa protein harboring two extra-catalytic domains, namely, GST-like and WHEP domains (Fig. 1a) [21]. High level of MARS1 in breast cancer and NSCLC patients is associated with poor clinical outcomes; in bile duct adenocarcinoma, enhanced expression of MARS1 correlates with cell proliferation, migration, and epithelial-mesenchymal transition [32–34]. At the molecular level, MARS1-dependent stabilization of CDK4 contributes to breast cancer progression [35]. Furthermore, by binding and inhibiting ATR, a DNA repair protein, it reduces DNA damage-induced apoptosis resulting in colorectal cancer cell growth [35]. A somatic frameshift mutation in exon 3 of MARS1 was identified in colorectal and gastric cancer, however a potential pathological role has not yet been shown [36]. Finally, unexpected nucleolar localization of MARS1 regulates ribosomal RNA production that can contribute to tumorigenesis [37]. MARS1 expression has potential as a diagnostic marker as dual staining of MARS1 and CD45 has been proposed as a marker for NSCLC [38], and dual immunofluorescence staining of MARS1 and AIMP2-DX2 (see below) has shown utility for detection of lung cancer [39]. The evolutionary addition of the WHEP domain in both MARS1 and EPRS1, combined with the correlation of both proteins as diagnostic markers in cancer, suggests the domain has potential as a therapeutic target.

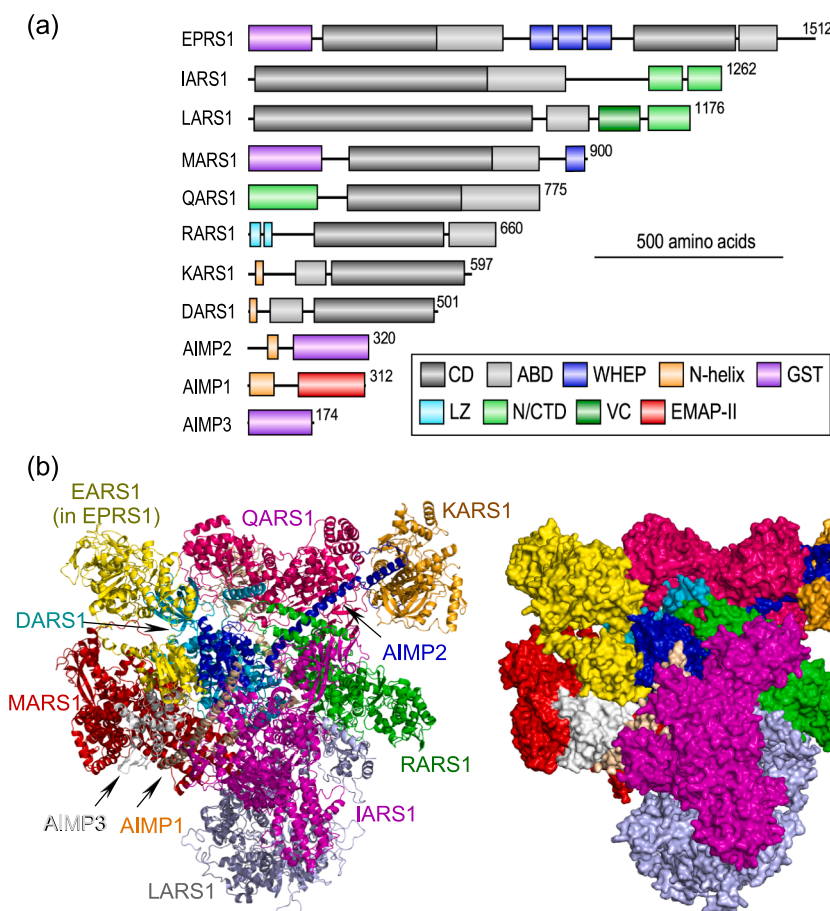


Fig. 1. Mammalian MSC Constituents and Structure. (a) Domain organization of the MSC-resident AARs and auxiliary proteins (AIMPs). Each domain is highlighted in different color. Catalytic domains (CD, dark gray), anticodon binding domains (ABD, light gray), WHEP domains (cyan), lysine-rich N-helical domain (N-helix, orange), GST-like domains (GST, purple), leucine zipper (LZ, cyan), N- and C-terminal domains (N/CTD, light green), vertebrate C-terminal (VC, green), and EMAP-II (red) are indicated. (b) 3-dimensional models of human holo-MSC as obtained from cross-linking mass spectrometry studies. Ribbon (left) and space filled (right) models of MSC are illustrated.

Glutamyl-tRNA synthetase (QARS1)

Mutations in QARS1, an ~88 kDa protein, are mostly associated with neurological disorders [40], and reports of cancer-association are limited. Mass-spectrometric analysis of inactive aggregates of P53 tumor suppressor, that provides chemoresistance in serous ovarian carcinoma cells, revealed preferential interaction with QARS1 (among other proteins) compared to soluble, active p53, and thus is predicted to contribute to chemoresistance [41]. Moreover, glutamine-dependent binding of QARS1 inactivates the pro-apoptotic protein ASK1, and thus the synthetase might provide the link between glutamine and its known apoptosis suppressor activity [42]. Information on the role of QARS1 in cancer progression is limited, and more studies will be necessary to elucidate its potential role in cancer pathology.

Leucyl-tRNA synthetase (LARS1)

The ~135 kDa LARS1 has been implicated in migration and proliferation of lung cancer cells [43]. Recent studies reveal a critical role of LARS1 in activation of mTORC1, which is upregulated in several cancers and might present an as-yet unexplored link between the synthetase and tumorigenesis [44,45]. LARS1, in coordination with Rag GTPase, acts as a leucine sensor to activate mTORC1 [46–48]. Notch3- and PHD1-mediated induction of LARS1 directs mTORC1 activation and adipogenesis, which in turn can contribute to cancer progression [49, 50]. Recent crystallographic elucidation of the structure of mammalian LARS1 is likely to accelerate the search for low molecular weight inhibitors for potential anti-cancer therapy [51]. Although, LARS1 has been studied extensively, a direct association with cancer progression and studies in primary or patient tissues samples is lacking. Future studies will determine if LARS1, indeed, is involved in cancer pathogenesis.

Arginyl-tRNA synthetase (RARS1)

Marked tumorigenic activity of RARS1 has been reported. About a 2-fold increase in activity of the ~75 kDa RARS1 was shown in malignant rat hepatoma cells characterized by increased growth rate compared to healthy rat liver cells [52]. Reduced expression of microRNAs miR-15a and miR-16-1 in pituitary adenomas, due to regional deletion, increases expression of RARS1, which in turn diminishes extracellular secretion of the tumor suppressor, AIMP1, and accelerates tumor growth [53,54]. The possibility that RARS1 acts as a “sponge” trapping the tumor suppressor AIMP1 is a mechanism that needs further investigation. We and others have shown that RARS1 and AIMP1 interact within the MSC (Fig. 1b) [18,55] however, the possible role of RARS1 in releasing AIMP1 from the MSC has not been investigated. Following chromosomal translocation in nasopharyngeal carcinoma (NPC) fusion of *RARS1* with *MAD1L1* induces cancer stem cell-like characteristics driving head and neck tumor growth [56,57].

Aspartyl-tRNA synthetase (DARS1)

~58 kDa *DARS1* was shown to be an oncogene driving progression of the most prevalent type of renal cell carcinoma, namely, clear cell renal cell carcinoma (ccRCC). *DARS-AS1* is a long noncoding RNA positioned near the *DARS1* gene [58]. *DARS-AS1* upregulates *DARS1* by sequestering its inhibitor, miR-194-5p, thereby contributing to malignancy in ccRCC. Likewise, *DARS-AS1* is oncogenic in acute myeloid leukemia (AML) where it exhibits a negative correlation with the prognostic factor, miR-425, regulating TGF- β expression [59]. *DARS-AS1* also accelerates proliferation of cervical cancer cells via miR-638-5p/JAG1 axis to regulate Notch pathway [60]. Interestingly, single nucleotide polymorphisms (SNPs) in *DARS1* are associated with altered asparaginase activity, and might contribute to asparaginase sensitivity in childhood acute lymphoblastic leukemia [61].

Lysyl-tRNA synthetase (KARS1)

~68 kDa KARS1 is highly over-expressed in multiple cancers [62–64]. MSC disassociation and membrane re-localization of KARS1 is associated with dissemination of small groups of cells from colon cancer spheroids; the KARS1/ERKs/paxillin signaling axis is required for this dissemination [65,66]. KARS1 promotes cell-cell and cell-extracellular matrix adhesion required for colon cancer cell migration [67]. Likewise, KARS1 interaction with laminin receptor 67LR prevents ubiquitin-dependent degradation of the receptor and promotes cancer progression [68]. Caspase-8 mediated N-terminus cleavage of KARS1 induces disassociation from the MSC and binding to syntenin which facilitates exosomal secretion, and ultimately macrophage migration and inflammation [69]. In spheroids, KARS1 remodels the tumor microenvironment by inducing M2 macrophage polarization contributing to tumor metastasis [70]. Ser207 phosphorylation of KARS1 by epidermal growth factor receptor (EGFR), primarily in NSCLC patients with EGFR mutations, induces nuclear translocation of KARS1, and is associated with improved mean disease-free survival [71]. In melanoma cells free KARS1 can generate diadenosine tetraphosphate, i.e., Ap₄A, which binds HINT1, thereby disrupting its interaction with microphthalmia transcription factor (MITF), resulting in MITF-dependent transcription and oncogenic activity [72,73]. Furthermore, KARS1 SNPs are associated with DNA-damage response and increased cancer occurrence [74,75]. The abundant evidence showing pleiotropic activities of post-translationally modified KARS1 that influence multiple cancer progression pathways, suggests it is an important MSC AARS involved in carcinogenesis, and a likely target for therapeutic intervention

Aminoacyl-tRNA synthase complex-interacting protein 1 (AIMP1)

AIMP1 is an ~34 kDa protein with tumor suppressor activity that distinguishes it from other MSC constituents. Purified AIMP1 has potent anti-tumor activity as shown in mouse xenograft models, and inhibition of cell cycle progression in gastric cancer-bearing mice [76,77]. AIMP1 administration increases expression of the potent tumor-suppressing cytokines TNF- α and IL-1 β [77]. With a sub-clinical dose of paclitaxel, AIMP1 combination therapy reduces growth of stomach cancer cells and lung cancer xenografts [76]. The tumor suppressor activity of AIMP1 is supported by its reduced expression in gastric and colorectal cancer tissues compared to adjacent normal tissue, as well as under hypoxic conditions where its high expression is associated with diminished risk of glioblastoma [78–80]. In pituitary adenomas RARS1 regulates AIMP1 secretion where it exerts potent anti-tumor activity [54]. Proteolytic cleavage of AIMP1 generates the multi-functional inflammatory cytokine endothelial monocyte-activating polypeptide II (EMAP II) [54] (discussed in detail below). AIMP1 has been associated with poor survival in patients with head and neck squamous cell carcinoma [81]. In laryngeal squamous cell carcinoma AIMP1, in cooperation with leukotriene A4 hydrolase (LTA4H), promotes cell proliferation, migration, and invasion by binding fascin actin-bundling protein 1 [82]. As both full-length AIMP1 and its cleaved product EMAP II exhibit anti-cancer activities, strategies have been developed to improve the stability of the recombinant proteins, primarily by reducing aggregation [83].

AIMP1 influences diverse immune response. It negatively regulates the expansion of myeloid-derived suppressor cells (MDSCs) involved in immune suppression in breast tumor-bearing mice, and reduces their differentiation and induction of Treg cell differentiation [84]. Alternatively, AIMP1 stimulates anti-tumorigenic NK cells in a TNF- α -dependent manner, and TH1 polarization by regulating cytokine and costimulatory molecule expression as well as p38 MAPK signaling [85,86]. It stimulates antigen-presenting cells to secrete IL-12 by increasing NF- κ B occupancy on the IL-12 promoter leading to enhanced TH1 responses [87]. In fact, anti-CD3 single-chain Fv fusion with AIMP1 serves as a DNA adjuvant enhancing TH1 cell-mediated immune

responses against cancer cells [88]. Mouse fibroblasts genetically modified to express AIMP1 and costimulatory B7.1 exhibit potent cytotoxic activities against OVA-expressing EG7 tumor cells [89]. The anti-tumor activity in multiple cell lines, coupled with promising animal studies, suggests the potential for AIMP1 as a promising target for anti-cancer therapeutics.

Aminoacyl tRNA synthase complex interacting protein 2 (AIMP2)

AIMP2 is a 38 kDa protein with tumor suppressive activity similar to AIMP1. Mice heterozygous or homozygous for AIMP2 deletion are highly susceptible to tumor formation [90]. Oxidative stress induces AIMP2 disassociation from the MSC and relocalization to the nucleus where it interacts with FUBP1 (far upstream element binding protein) resulting in the expression of USP29 (ubiquitin-specific peptidase 29) which stabilizes p53 by ubiquitin cleavage [91]. AIMP2 expression is downregulated in gastric and colorectal cancer [78]. In liver cancer cells, treatment with prostaglandin E2, increases FUSE binding protein (FBP) and reduces AIMP2 expression, tilting the balance towards higher FBP expression, in turn inducing c-Myc [92]. TGF- β induces S156 phosphorylation of AIMP2 in HeLa cells, inducing release from the MSC and nuclear re-localization where it binds Smurf2 protein enhancing FBP ubiquitination and degradation [93]. AIMP2 regulates the level of intestinal stem cells (ISC), which in excess can cause colorectal cancer, by inhibiting the WNT/ β -catenin signaling pathway [94]. Following fusion in nasopharyngeal carcinoma, RARS1-MAD1L1 interacts with AIMP2, thereby activating the oncogenic FUBP1/c-Myc pathway [57]. Also, AIMP2 has been identified as a hub associated with poor survival in tongue squamous cell carcinoma [95]. Although, AIMP2 exhibits robust anti-tumorigenic activities in cell line models, its activity in stem cell maintenance and RARS1-MAD1L1-mediated activation of the FUBP1/c-Myc pathway indicates its role in cancer pathology still remains uncertain.

Aminoacyl tRNA synthase complex interacting protein 3 (AIMP3)

The smallest protein constituent of the MSC, ~20 kDa AIMP3, is a tumor suppressor that induces the p53 response to DNA damage, thereby preventing oncogenic stress and cell transformation. Haplo-deficient AIMP3 cells are more susceptible for transformation by oncogenes due to altered ATM and ATR kinase activation [96]. Tissue microarray revealed that expression of AIMP3, like the other AIMP2s, is significantly repressed in several cancer tissues and correlates with patient survival [78,97]. A SNP analysis of Chinese test subjects identified the rs12199241 allele which reduces AIMP3 expression and is associated with increased DNA damage, possibly due to reduced activity of the DNA damage-repair pathway [75]. Likewise, in invasive bladder cancer, AIMP3 expression is suppressed resulting in increased ionizing radiation resistance of these cells [97]. Consistent with these findings, AIMP3 knockout mice exhibit significant loss of homologous recombination and DNA damage, accompanied by acute radiation syndrome-like phenotype, including hypertrophy of hematopoietic cells, and organ and intestinal failure [98]. In NSCLC cells, miR-96-5p reduces AIMP3 expression leading to reduced p53 response and enhanced proliferation and migration of cancer cells in vitro [99]. Evidence for a pro-tumorigenic role of AIMP3 is uncommon; however, its deletion in mice is embryonically lethal due to accumulated DNA damage in embryonic stem cells and loss of self-renewal and differentiation capability [100]. It is tempting to speculate that AIMP3 might be involved in self-renewal of cancer stem cells with deleterious outcome.

Variants of MSC constituents and their role in cancer progression

Endothelial-monocyte-activating polypeptide-II (EMAP-II)

EMAP-II is a 22 kDa proteolytically-cleaved fragment of AIMP1, first

purified from conditioned medium of methychoanthrene A-induced murine fibrosarcoma cells, and exhibiting endothelial cell (EC)-activating and monocyte pro-migratory properties [101,102]. EMAP-II overexpression renders TNF (tumor necrosis factor)- α -resistant soft tissue sarcoma sensitive to TNF- α therapy, and is dependent on TNF-receptor-1 relocalization from Golgi storage pools to the cell plasma membrane [103–105]. In prostate adenocarcinoma cells, chemotherapeutic agents induce EMAP II expression, thereby potentiating localized activation of host cell effector mechanisms, as well as anti-angiogenic and pro-apoptotic activities in melanoma lines [106, 107]. EMAP-II binds the EC α 5 β 1 receptor directing its internalization and interaction with PSMA7, a component of the proteasome degradation pathway that induces HIF-1 α degradation [108]. Tumor-bearing mice treated with a combination of EMAP-II and photodynamic therapy (PDT), in which photochemical generation of cytotoxic singlet oxygen leads to localized tumor destruction, significantly reduces tumorigenesis compared to PDT alone [109]. Elevated EMAP-II expression correlates with improved survival of glioblastoma patients, and following trans-retinoic acid treatment of squamous carcinoma cells, is thought to be a mechanism of retinoid chemoprevention [110, 111]. Recombinant EMAP-II therapy in mice retards tumor growth by targeting vascular endothelium, and possibly inducing cytoskeletal remodeling [112,113]. EMAP-II increases the blood-tumor barrier permeability in glioblastoma, and the effectiveness of chemotherapy, by interacting with the ATP synthase α subunit and altering tight junction complexes between brain EC [114,115]. In glioblastoma stem cells, EMAP-II regulates G2/M cell cycle arrest by inhibiting simultaneous activation of the PI3K/Akt pathway activation and FoxO1 [116,117]. Also in glioblastoma stem cells, combination therapy of EMAP-II with temozolomide upregulates miR-590-3p and represses the PI3K/AKT/mTOR signaling pathway [118]. In primary uveal melanoma, expression of EMAP-II correlates with enhanced expression of EC ICAM-1 which causes macrophage activation and localized vascular damage [119]. In certain situations, for example in colorectal cancer, EMAP-II exhibits tumor-protective activity, facilitating tumor evasion of immune surveillance by inducing apoptosis in activated lymphocytes and ECs [120–122]. In addition, hypoxia facilitates EMAP-II-dependent lymphocyte killing and immune evasion [123].

AIMP1 and its proteolytic cleavage product EMAP-II both exhibit anti-tumorigenic properties; however, there are substantial differences between their functions. AIMP1, unlike EMAP-II, upregulates pro-inflammatory chemokines, e.g., IL-8, MIP-1, MIP-2 α , MCP-1, and IL-8, among others [124]. EMAP-II is secreted from apoptotic or necrotic cells following caspase-mediated cleavage [125], possibly suggesting a desperate effort by host cells to defend against cancerous cells.

AIMP2-DX2

AIMP2-DX2, a splicing variant of AIMP2 lacking exon 2, is pathologically associated with cancer and is induced by carcinogen treatment, in contrast to the tumor suppressive activity of the parent AIMP2 [126]. For example, AIMP2-DX2 overexpression is associated with increased proliferation, migration, and invasion of nasopharyngeal carcinoma cells [127]. Autoantibodies against AIMP2-DX2 in sera of lung cancer patients is associated with poor outcomes [128]. In contrast, down-regulation of AIMP2-DX2 inhibits chemo-resistant ovarian and lung cancer cell growth [129,130]. In addition to influencing solid tumor growth, the ratio of AIMP2-DX2/AIMP2 expression correlates with poor prognosis in hematological cancers [131].

With respect to molecular mechanism, AIMP2-DX2 fails to associate with the MSC, and competitively binds p53 to interfere with pro-apoptotic activities of AIMP2 [131]. Its interaction with HSP70 increases cell transformation and chemical intervention suppresses cancer cell growth in vitro and in vivo [132]. Likewise, targeted degradation by ribozymes efficiently reduces cancer cell growth [133]. AIMP2-DX2 knockdown in mice reduces lung cancer progression by inhibiting the

AKT1-mTOR-p70S6K1 signaling [134]. AIMP2-DX2 is an example of how tumor cells take advantage of host cellular machinery to generate novel proteins supporting their own survival.

Threonyl t-RNA synthetase-like protein 2 (TARSL2)

TARSL2 is the result of a gene duplication of TARS1 bearing a novel N-terminal extension that directs inclusion in the MSC [135,136]. Little is known about the variant, but it has been observed in pediatric brain tumor cells [137]. Moreover, pathway analysis revealed an association of TARSL2 with poor bladder cancer outcome [138]. As a newly-identified MSC constituent, more studies are required to elucidate its tumor-related function.

Function of the MSC

Despite extensive investigation for several decades, the function of the MSC remains uncertain [139,140]. Inclusion in the MSC can contribute to stability of constituents [141]. Interaction of the MSC with ribosomes has been proposed to enhance translation efficiency due to direct channeling of charged tRNA's to the emerging polypeptide chain [142,143]. However, MSC association does not appear to regulate catalytic activity of constituent tRNA synthetases, and thus alternative hypotheses have been suggested [16]. Appendage of domains during evolution that are absent in prokaryotic AARs can facilitate protein-protein interactions, particularly with other MSC constituents, but also can dictate non-canonical (i.e., moonlighting) functions unrelated to their primary function in interpretation of the genetic code [19, 144,145]. MSC has been proposed to be a "depot" that sequesters constituents that in free form might exhibit detrimental activities [14,15]. In contrast, MSC constituents released in a stimulus-dependent manner can exhibit condition-specific, beneficial functions; because release does not require mRNA or protein synthesis, the mechanism has the dual efficiencies of speed as well as minimal energy requirement.

MSC: Pro- or anti-tumorigenic?

As multiple AARs are upregulated in cancer cells, it is tempting to speculate it as a pro-tumorigenic consequence of rapid cell-division requiring highly active translational machinery. However, upregulation of only selected AARs in specific cancers, while maintaining basal expression in others, argues against this mechanism. The correlation between MSC release of AARs (discussed below) and their pro-tumorigenic properties also suggests cancer-causative activity. The acquisition of appended domains allows the MSC-associated AARs to perform both cancer-causing functions and enhanced protein synthesis, which together can stimulate tumor growth.

Contrary to the MSC-resident AARs, the auxiliary proteins AIMP1–3 primarily exhibit anti-tumorigenic functions. These conflicting observations ambiguate the overall ex-translational role of the MSC. The AIMP proteins lack enzymatic activities and they are generally considered to be scaffolding proteins involved in the assembly and structure of the large MSCs found in higher eukaryotes, but not in prokaryotes bearing much smaller MSCs [10]. Nonetheless, the AIMP proteins participate in multiple protein-protein interactions, primarily with appended domains of MSC-resident AARs [18]. The important role of AIMP proteins in AAR sequestration within the MSC has been shown in studies in which AIMP knockdown leads to AAR release [141]. Thus, AIMP proteins exhibit dual anti-tumorigenic functions – exerted both as extra-MSC activities and by preventing release of pro-tumorigenic AARs from the MSC. Thus, the pro- or anti-tumorigenic activity of the MSC is likely to be stimulus- and condition-dependent, with the overall activity determined by the specific constituents released.

Apart from the nine MSC-associated AARs, the eleven extra-MSC AARs are associated with several diseases including cancer [4,146]. Similar to MSC-associated AARs, many extra-MSC AARs also acquired

non-catalytic, appended domains during evolution, provoking a question; why are these AARs not incorporated in the MSC or MSC-like multi-protein complexes? Many of these extra-MSC AARs are secretory in nature and have anti-tumorigenic properties contrary to the MSC-associated AARs [147–153]. Extra-MSC localization might allow for more rapid or efficient transport across the plasma membrane. Also, sequestration of MSC-resident AARs might reduce pro-tumorigenic activities, unlike the anti-tumorigenic activities of extra-MSC AARs. It is possible that during evolution, when the AARs were gaining additional domains, the auxiliary proteins selectively sequestered the pro-tumorigenic/deleterious AARs into a multi-protein MSC, thereby regulating their non-canonical functions without affecting their canonical function in translation [16].

Factors determining constituent release from the MSC

Post-translational modifications (PTMs)

Phosphorylation is the principal PTM that drives release of individual components from the MSC (Fig. 2). In the first known example, IFN- γ activation of macrophages causes Cdk5- and S6K1-dependent dual phosphorylation of human EPRS1 at Ser886 and Ser999, thereby stimulating its release from the MSC [27,154]. Cdk5 and S6K1 are upregulated in multiple cancers, and might contribute to the role of EPRS1 in tumorigenesis [155,156]. Insulin stimulates phosphorylation of EPRS1 in adipocytes, but its connection to cancer has not been explored [157]. Likewise, EPRS1 Ser990 phosphorylation following viral infection induces release from the MSC to inhibit viral replication, but the role of this modification in cancer is unknown [158]. Ser662 phosphorylation of MARS1 by GCN2 following UV irradiation induces a conformational change that causes AIMP3 release from the MSC; subsequent interaction with p53 in the nucleus induces tumor suppressive activities (Fig. 2) [159]. In contrast, MARS1 phosphorylation by ERK1/2 at Ser209 and Ser825 does not induce MSC release, but causes mis-acylation, a phenomenon associated with cancer progression [160]. Proteomic analysis of DARS1 identified phosphorylation sites at Tyr239 and Ser249 and six acetylation sites at Lys55, 110, 213, 241, 330, and 453, although their impact on localization is unknown [161]. Likewise, structural studies identified DARS1 Ser146 phosphorylation in human cells, but the proposed role in MSC release has not been validated [162]. Ser207 phosphorylation of KARS1 induces release from the MSC and relocalization to the nucleus where it binds and activates microphthalmia-associated transcription factor (MITF), a β -protein implicated in melanoma (Fig. 2) [163,164]. EGFR-mediated Ser207 phosphorylation of KARS1 in lung cancer cells and in NSCLC patients has been described, and interestingly, phospho-KARS1 immunostaining is associated with better prognosis in these patients [71]. Thr52 phosphorylation causes KARS1 re-localization from the MSC to the plasma membrane where it inhibits ubiquitin-dependent degradation of the 67-kDa laminin receptor, thereby enhancing cell migration [68]. DNA damage-mediated phosphorylation of AIMP2 by JNK causing re-localization from the MSC to the nucleus where it binds and stabilizes p53 [165]. Similarly, Ser156 phosphorylation of AIMP2 by p38 MAPK in HeLa cells causes release from the MSC and anti-tumorigenic activity following interaction with nuclear Smurf2 (Fig. 2) [93]. Likewise, AIMP3 phosphorylation by ERK is linked to anti-tumorigenic activities, however, its release from the MSC remains to be explored [96]. Although phosphorylation is the principal known PTM inducing MSC constituent release, modifications yet to be determined are worthy of consideration in future studies.

Protease-mediated cleavage

Biochemical studies have shown that controlled proteolysis can generate active mammalian AAR proteoforms (Fig. 2) [142]. Yeast two-hybrid screen showed calpain-2 interacts not only with LARS1, but also cleaves other MSC constituents including EPRS1, MARS1, DARS1,

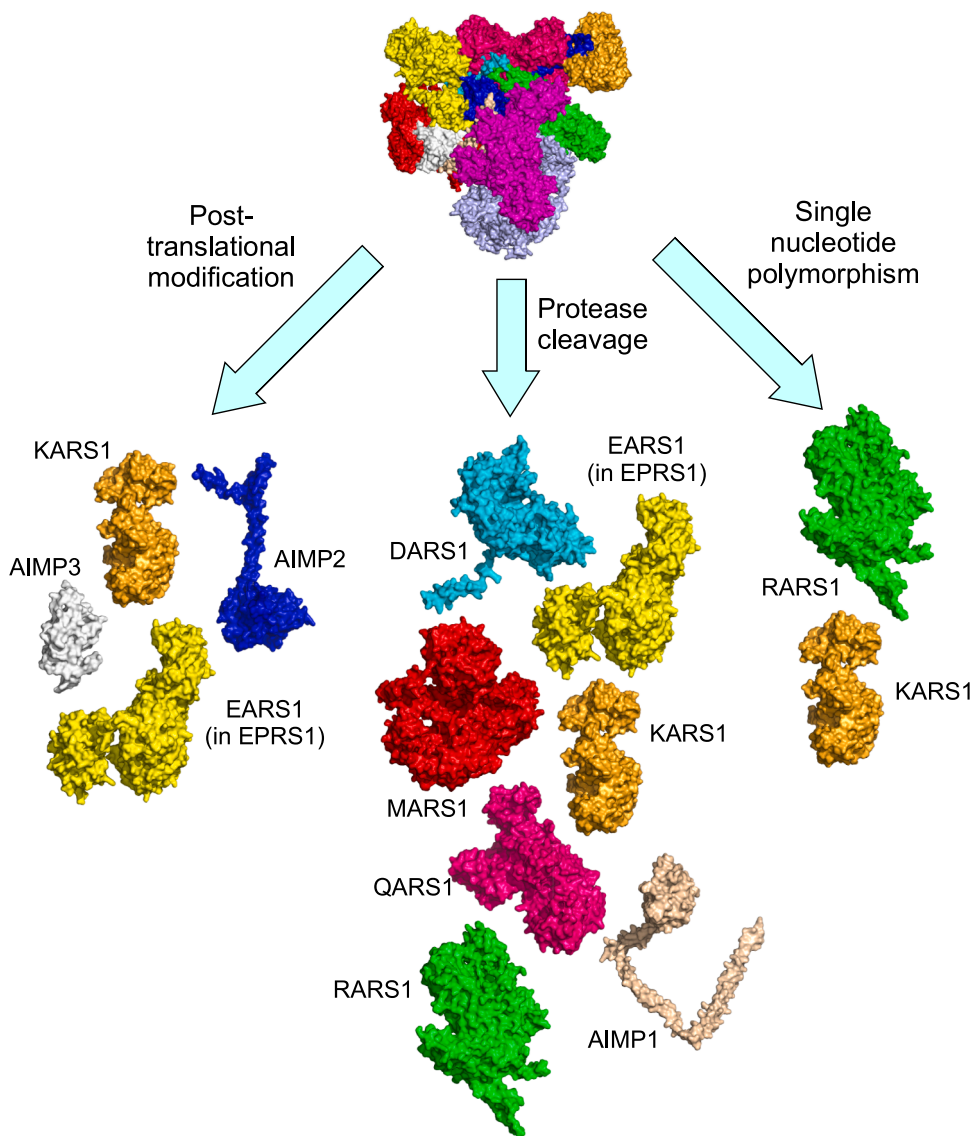


Fig. 2. Environmental Cues Mediate Release of AARSs from the MSC by Multiple Mechanisms. Experimentally validated constituents released from the MSC are depicted. KARS1, EPRS1, AIMP2, and AIMP3 are released from the MSC following post-translational modifications, primarily phosphorylation. EPRS1, DARS1, MARS1, KARS1, QARS1, RARS1, and AIMP1 dissociate from the MSC following protease-mediated cleavage. Single nucleotide polymorphisms mediate MSC release of RARS1 and KARS1.

QARS1, RARS1, and AIMP1, resulting in generation of fragments that escape the MSC (Fig. 2) [166]. Similarly, caspase 7-mediated cleavage releases the EMAP-II domain of AIMP1 that stimulates migration of mononuclear phagocytes [167]. AIMP1 cleavage by elastase in apoptotic U937 cells generates p43-derived apoptosis release factor [168]. N-terminal truncation of QARS1 by calpain prevents MSC incorporation and directs nuclear localization [166]. Caspase-8-mediated cleavage of the N-terminus of KARS1 induces release from the MSC, secretion via exosomes, and inflammation (Fig. 2) [69]. Caspase-mediated cleavage at EPRS1 Asp929 in the third WHEP domain generates neoEPRS1, an N-terminal proteoform of unknown in vivo function [169].

Single nucleotide polymorphisms/point mutations in MSC constituents

Multiple single amino acid changes in EPRS1, LARS1, DARS1, IARS1, and MARS1 have been reported but MSC localization and their potential roles in cancer remain to be explored [170–173]. Interestingly, several mutations in DARS1 (Arg460His, Pro464Leu) that cause hypomyelination with brain stem and spinal cord involvement and leg spasticity were found that might induce release from the MSC [172]. In the case of QARS1, R403W mutation causes neurodegenerative disease; however,

localization of the mutant remains to be explored [40]. D2G mutation in the RARS1 N-terminus releases it from the MSC and causes Pelizaeus-Merzbacher disease (Fig. 2) [174]. In KARS1, P200L and F263V mutations reduce its affinity for AIMP2 and the MSC, and causes optic neuropathy (Fig. 2) [175]. The KARS1 P200L mutation site is close to Ser207, the residue that when phosphorylated causes release from MSC, consistent with a role of local structure in MSC retention. Other neurological disease-causing KARS1 mutations including Phe127Leu and Pro297Ala, reduce dimerization; as KARS1 is present as a dimer in the MSC, reduced dimerization might influence its localization [176]. Mutations in AIMPs 1 and 2 have been observed in neurodegenerative diseases, whereas multiple point mutations in AIMP3 (Thr35/Ser40, Thr76, Thr80, Ser87, Val106 and Arg144) are seen in chronic myeloid leukemia patients. Few of these mutations reduce the affinity of AIMP3 for ATM but nor for MARS1, but their altered function or localization has not been investigated [177–179]. Most AARS mutations mentioned here have been associated with non-cancer pathologies. The adaptation of whole exome sequencing likely will facilitate identification of additional AARS mutations, and their potential association with cancer incidence and progression. Whether the mutations discussed here predispose patient's cancer is not known, and cell-based studies where similar mutation are introduced, for example by CRISPR/Cas9 technology, will

clarify MSC localization of these mutant proteins along with additional functions, and further illuminate the role of MSC release of constituents on tumorigenic functions.

Role of MSC structure in constituent release

The assembly and structure of the MSC can provide important clues to mechanisms of constituent release. A collection of sub-complexes has been revealed by biochemical and structural studies, showing key interactions, but the role of these complexes in MSC assembly is unclear [21,55,180]. According to a recent 3-dimensional model, all of the constituents have substantial surface exposure [18]. The structure is organized in a way that many constituents have limited interactions with just a few neighbors, possibly facilitating release. Post-translational modification, most often phosphorylation can alter the structure of a constituent or interfere with a critical binding domain interface. The latter is exemplified by phosphorylation of KARS1 in the domain that interacts with the N-terminus of AIMP2, thereby inducing a steric clash, release from the MSC, and subsequent entry into the nucleus [163]. In nearly all cases only a small fraction of a constituent is released. It is unclear why only a small amount is released as artificial exclusion of the entire pool of a constituent from the MSC does not alter protein synthesis efficiency [16]. Possibly the signaling pathway inducing the post-translational modification is limiting or transitory. EPRS1 release is an exception to this principle since at least half is released from the MSC upon stimulus-dependent phosphorylation [27,157]. In either case, the amount of a protein released post-modification is sufficient to trigger robust cellular activities, including effecting cancer progression.

AARSs and immune regulation: a potential link to cancer development and progression

Immune dysregulation and inflammation are major mechanisms influencing cancer incidence, progression, and dissemination, and chronic inflammation due to overactive immune cells is associated with an increased risk of cancer malignancy [181,182]. Tumor-associated macrophages in particular have essential roles in tumor progression [183]. AARSs are influenced by diverse immunological conditions and stresses within the tumor microenvironment [184]. For example, TNF- α -induced secretion of KARS1 binds macrophages, feeding forward to exacerbate TNF- α secretion thus amplifying the inflammatory state [185]. Similarly, AIMP1 induces macrophage expression of multiple inflammatory cytokines in a MAPK and NF- κ B-dependent fashion [124]. CD23, a cell-surface receptor for AIMP1 further induces TNF- α secretion [186]. EMAP2, the secreted proteolytic product of AIMP1, induces an acute inflammatory response and recruit macrophages [187]. The high affinity of T-cell receptor (TCR) for microbial peptide:MHC class II complex upregulates AIMP3 and IL-2R proteins, promoting Th1 cell differentiation and inflammation [188]. EPRS1, upregulated in multiple cancers, exhibits an anti-inflammatory function in which it participates in translational silencing of inflammation-related agents in myeloid cells, for example VEGFA [27,29]. EPRS1 activates TGF- β /STAT signaling, and TGF- β induces Th17 cell differentiation a principal effector of cancer progression [189–191]. Likewise, halofuginone, a potent inhibitor of the prolyl-tRNA synthetase activity of EPRS1, suppresses inflammatory response by inhibiting Th17 cell differentiation [192]. Inhibition of MARS1 suppresses *Drosophila* inflammatory and immune response genes and mutations in *DARS1* causes leukoencephalopathy along with spinal cord abnormalities mimicking neuro-inflammatory disease [172,193]. Homozygous mutations in *LARS1* cause very early-onset inflammatory bowel disease associated with T-cell dysfunction [194]. Many AARSs likely have multi-faceted roles, alone or in concert with other proteins, driving cancer progression where it can function as a proto-oncogene by driving specific signaling pathways, and can also dysregulate the immune environment that by itself can promote cancer.

Anti-cancer therapeutics targeting AARSs

MSC AARSs can stimulate initiation and progression of multiple cancers, and thus therapeutics targeting these AARSs are under development [5]. These drugs can target either AARSs catalytic activity within the tumor or undesirable protein-protein interactions that drive tumorigenesis. Halofuginone, an inhibitor of the prolyl-tRNA synthetase catalytic activity of EPRS1 [195] inhibits breast and prostate cancer metastasis by reducing TGF- β and BMP-regulated pathways, and sensitizes lung cancer for chemotherapy by suppressing NRF2 accumulation [196,197]. Although, a major mechanism of halofuginone function is inhibition of collagen biosynthesis, it also activates the amino acid starvation response in cancer cells due to its inhibition of prolyl-tRNA synthetase activity [195,198,199,200]. As EPRS1 is over-expressed in many cancers, inhibition of prolyl-tRNA synthetase activity by halofuginone might contribute to its tumor-suppressive activity; however, a direct link between halofuginone-mediated inhibition of EPRS1 and reduction in cancer cell growth has not been shown. Xanthoangelol and 4-hydroxyderricin bind EPRS1 and prevent its interaction with SCYL2, thereby abrogating the WNT/GSK-3 β / β -catenin signaling pathway and reducing patient-derived xenograft tumor growth in mice [26].

Small molecules derived from quinoline, 1,3-benzoxazine, and 1,3-oxazine compete with methionine and adenosine binding sites in MARS1, and are effective in suppressing AF59 and HCT116 cell proliferation [201]. Inhibitors of LARS1, e.g., AN2690 and its derivatives, exhibit anti-tumor activity in U2OS and SKOV3 cells by activating p21-mediated cell apoptosis [202]. Similarly, the LARS1 inhibitor BC-LI-0186 at nanomolar concentration exhibits potent anti-tumor activity against lung cancer cells [203]. Recent studies highlight the role of LARS1 in mTORC1 activation and competitive inhibitors of LARS1, e.g., leucinol and leucyladenylate sulfate derivatives, prevent leucine-mediated activation of mTORC1 [204–209]. Similarly, BC-LI-0186 prevents LARS1 lysosomal localization and mTORC1 activation by blocking RagD-LARS1 interaction [51]. Small molecule inhibitors against KARS1, e.g., SL-1910, reduce migration of MDA-MB-231 cells, whereas BC-K_YH16899 inhibits the interaction of KARS1 and 67 kDa laminin receptor, thereby suppressing membrane localization in cells and metastasis in mouse models [210,211]. Inhibition of caspase-8-mediated cleavage of KARS1 abrogates its secretion via exosomes and reduces inflammation [69]. Thiazolo[5,4-b]pyridines (SL-1910) is a KARS1 inhibitor that reduces cell migration and prevents tumor metastasis in mice [210]. L-canavanine is a structural analog of L-arginine that as an AARS1 substrate is competitively incorporated into nascent proteins. L-canavananyl-containing proteins are less basic than wild-type, thereby influencing essential protein structures and ionic interactions, resulting in cell death. Canavanine is specifically sequestered by the pancreas, and is predicted to be useful as an adjuvant therapy for pancreatic cancer [212]. Small molecule inhibitors targeting AIMP2-DX2 mRNA, e.g., BC-DX101, degrade the transcript and in reduce AIMP2-DX2 level and tumor size in mice [213]. In lung carcinogenesis, AIMP2-DX2 induction by oncogenes promotes drug resistance by binding and inhibiting p14/ARF. SLCB050, blocks the interaction between AIMP2-DX2 and p14/ARF in vitro, and in vivo reduces the viability of small cell lung cancer cells in a mouse model of K-ras-driven lung tumorigenesis [214]. BC-DX1-843 is a sulfonamide-based drug that selectively inhibits AIMP2-DX2 binding to HSP70 resulting in its selective Siah-1-mediated ubiquitination and degradation in lung cancer cells [132,215]. Pyrimethamine is an anti-parasite drug that also induces selective, ubiquitin-mediated degradation of AIMP2-DX2, and suggests potential repurposing as an anti-tumor therapeutic agent [216]. As the association of AARSs with specific cancer types becomes stronger, investigation of existing inhibitors and generation of novel therapeutics is likely to accelerate. Several currently available inhibitors mentioned here are currently in clinical trials for cancer and other disorders [13]. However, much more basic research and translational development will be necessary to establish the potential of AARSs as therapeutic targets.

Concluding remarks

MSC constituents, particularly the AARs, are essential for cell viability under normal conditions due to their principal function in interpretation of the genetic code. However, it is becoming evident that the same constituents can induce pathology, including cancer progression. Recent appreciation of MSC structure and dynamics is contributing to our understanding of the mechanisms of activation of MSC constituents, and their potential to exhibit non-canonical moonlighting functions. Early and ongoing studies targeting MSC components show promising anti-tumor outcomes. Continued investigation will be necessary to understand the repertoire of functions that the MSC and its constituents perform, elucidate mechanisms of activation, and develop novel therapeutics that inhibit its constituent release, activity, or protein-protein interactions, and ultimately inhibit tumor initiation and progression.

Author contribution statement

Krishnendu Khan: Conceptualization, Writing – Original Draft, Writing - Review & Editing. **Valentin Gogonea:** Structural modeling of AARs and the MSC. **Paul Fox:** Conceptualization, Funding acquisition, Writing - Review & Editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

: The manuscript does not contain unpublished data.

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References

- [1] M. Ibba, D. Söll, Aminoacyl-tRNA synthesis, *Annu. Rev. Biochem.* 69 (2000) 617–650.
- [2] M. Mirande, Aminoacyl-tRNA synthetase family from prokaryotes and eukaryotes: structural domains and their implications, *Prog. Nucleic Acid Res. Mol. Biol.* 40 (1991) 95–142.
- [3] L. Ribas de Pouplana, P. Schimmel, Aminoacyl-tRNA synthetases: potential markers of genetic code development, *Trends Biochem. Sci.* 26 (2001) 591–596.
- [4] S. Kim, S. You, D. Hwang, Aminoacyl-tRNA synthetases and tumorigenesis: more than housekeeping, *Nat. Rev. Cancer* 11 (2011) 708–718.
- [5] Z. Zhou, B. Sun, A. Nie, D. Yu, M. Bian, Roles of aminoacyl-tRNA synthetases in cancer, *Front. Cell Dev. Biol.* 8 (2020), 599765. PMC7729087.
- [6] M. Guo, X.L. Yang, P. Schimmel, New functions of aminoacyl-tRNA synthetases beyond translation, *Nat. Rev. Mol. Cell Biol.* 11 (2010) 668–674. PMC3042954.
- [7] A. Arif, J. Jia, D. Halawani, P.L. Fox, Experimental approaches for investigation of aminoacyl tRNA synthetase phosphorylation, *Methods* 113 (2017) 72–82. PMC5253304.
- [8] I. Yoon, M. Nam, H.K. Kim, et al., Glucose-dependent control of leucine metabolism by leucyl-tRNA synthetase 1, *Science* 367 (2020) 205–210.
- [9] J. Ognjenovic, M. Simonovic, Human aminoacyl-tRNA synthetases in diseases of the nervous system, *RNA Biol* 15 (2018) 623–634. PMC6103678.
- [10] S. Havrylenko, M. Mirande, Aminoacyl-tRNA synthetase complexes in evolution, *Int. J. Mol. Sci.* 16 (2015) 6571–6594. PMC4394549.
- [11] J. Wang, I. Vallee, A. Dutta, Y. Wang, Z. Mo, Z. Liu, H. Cui, A.I. Su, X.L. Yang, Multi-omics database analysis of aminoacyl-tRNA synthetases in cancer, *Genes (Basel)* (2020), 11PMC7700366.
- [12] Z. Zhou, B. Sun, S. Huang, D. Yu, X. Zhang, Roles of aminoacyl-tRNA synthetase-interacting multi-functional proteins in physiology and cancer, *Cell Death Dis* 11 (2020) 579. PMC7382500.
- [13] N.H. Kwon, P.L. Fox, S. Kim, Aminoacyl-tRNA synthetases as therapeutic targets, *Nat. Rev. Drug Discov.* 18 (2019) 629–650.
- [14] P.S. Ray, A. Arif, P.L. Fox, Macromolecular complexes as depots for releasable regulatory proteins, *Trends Biochem. Sci.* 32 (2007) 158–164.
- [15] J.H. Kim, J.M. Han, S. Kim, Protein-protein interactions and multi-component complexes of aminoacyl-tRNA synthetases, *Top. Curr. Chem.* 344 (2014) 119–144.
- [16] H. Cui, M. Kapur, J.K. Diedrich, J.R. Yates, S.L. Ackerman, P. Schimmel, Regulation of ex-translational activities is the primary function of the multi-tRNA synthetase complex, *Nucleic Acids Res* 49 (2021) 3603–3616.
- [17] E.Y. Lee, S. Kim, M.H. Kim, Aminoacyl-tRNA synthetases, therapeutic targets for infectious diseases, *Biochem. Pharmacol.* 154 (2018) 424–434. PMC7092877.
- [18] K. Khan, C. Beleanu Gogonea, B. Willard, V. Gogonea, P.L. Fox, 3-Dimensional architecture of the human multi-tRNA synthetase complex, *Nucleic Acids Res* 48 (2020) 8740–8754. PMID: PMC7470956.
- [19] J. Jia, A. Arif, P.S. Ray, P.L. Fox, WHEP domains direct noncanonical function of glutamyl-prolyl tRNA synthetase in translational control of gene expression, *Mol. Cell* 29 (2008) 679–690. PMC2819395.
- [20] H.Y. Cho, H.J. Lee, Y.S. Choi, D.K. Kim, K.S. Jin, S. Kim, B.S. Kang, Symmetric assembly of a decameric subcomplex in human multi-tRNA synthetase complex via interactions between glutathione transferase-homology domains and aspartyl-tRNA synthetase, *J. Mol. Biol.* 431 (2019) 4475–4496.
- [21] H.Y. Cho, S.J. Maeng, H.J. Cho, et al., Assembly of multi-tRNA synthetase complex via heterotetrameric glutathione transferase-homology domains, *J. Biol. Chem.* 290 (2015) 29313–29328. PMC4705937.
- [22] L. Qi, B. Zhou, J. Chen, W. Hu, R. Bai, C. Ye, X. Weng, S. Zheng, Significant prognostic values of differentially expressed-aberrantly methylated hub genes in breast cancer, *J. Cancer* 10 (2019) 6618–6634. PMC6856906.
- [23] I. Katsyv, M. Wang, W.M. Song, X. Zhou, Y. Zhao, S. Park, J. Zhu, B. Zhang, H. Y. Irie, EPRS is a critical regulator of cell proliferation and estrogen signaling in ER+ breast cancer, *Oncotarget* 7 (2016) 69592–69605.
- [24] A.S. Beltran, L.M. Graves, P. Blancafort, Novel role of Engrailed 1 as a prosurvival transcription factor in basal-like breast cancer and engineering of interference peptides block its oncogenic function, *Oncogene* 33 (2014) 4767–4777. PMC4184217.
- [25] T. Kato, Y. Daigo, S. Hayama, N. Ishikawa, T. Yamabuki, T. Ito, M. Miyamoto, S. Kondo, Y. Nakamura, A novel human tRNA-dihydrouridine synthase involved in pulmonary carcinogenesis, *Cancer Res* 65 (2005) 5638–5646.
- [26] H. Liu, M. Fredimoses, P. Niu, et al., EPRS/GluRS promotes gastric cancer development via WNT/GSK-3 β / β -catenin signaling pathway, *Gastric Cancer* 24 (2021) 1021–1036.
- [27] P. Sampath, B. Mazumder, V. Seshadri, C.A. Gerber, L. Chavatte, M. Kinter, S. M. Ting, J.D. Dignam, S. Kim, D.M. Driscoll, P.L. Fox, Noncanonical function of glutamyl-prolyl-tRNA synthetase: gene-specific silencing of translation, *Cell* 119 (2004) 195–208.
- [28] B. Mazumder, P. Sampath, V. Seshadri, R.K. Maitra, P. DiCorleto, P.L. Fox, Regulated release of L13a from the 60S ribosomal subunit as a mechanism of transcript-specific translational control, *Cell* 115 (2003) 187–198.
- [29] P.S. Ray, J. Jia, P. Yao, M. Majumder, M. Hatzoglou, P.L. Fox, A stress-responsive RNA switch regulates VEGFA expression, *Nature* 457 (2009) 915–919. PMC3002251.
- [30] R. Mukhopadhyay, J. Jia, A. Arif, P.S. Ray, P.L. Fox, The GAIT system: a gatekeeper of inflammatory gene expression, *Trends Biochem. Sci.* 34 (2009) 324–331. PMC3637685.
- [31] E.Y. Lin, J.F. Li, L. Gnatovskiy, Y. Deng, L. Zhu, D.A. Grzesik, H. Qian, X.N. Xue, J. W. Pollard, Macrophages regulate the angiogenic switch in a mouse model of breast cancer, *Cancer Res* 66 (2006) 11238–11246.
- [32] E.Y. Kim, J.Y. Jung, A. Kim, K. Kim, Y.S. Chang, Methionyl-tRNA synthetase overexpression is associated with poor clinical outcomes in non-small cell lung cancer, *BMC Cancer* 17 (2017) 467. PMC5497355.
- [33] Q. Jin, G. Liu, B. Wang, S. Li, K. Ni, C. Wang, J. Ren, S. Zhang, Y. Dai, High methionyl-tRNA synthetase expression predicts poor prognosis in patients with breast cancer, *J. Clin. Pathol.* 73 (2020) 803–812. PMC7691814.
- [34] S.I. Jang, N.H. Kwon, B.J. Lim, et al., New staining method using methionyl-tRNA synthetase 1 antibody for brushing cytology of bile duct cancer, *Gastrointest. Endosc.* 92 (2020) 310–319, e316.
- [35] N.H. Kwon, J.Y. Lee, Y.L. Ryu, et al., Stabilization of cyclin-dependent kinase 4 by methionyl-tRNA synthetase in p16^{INK4a}-negative cancer, *ACS Pharmacol Transl Sci* 1 (2018) 21–31. PMC7089025.
- [36] S.W. Park, S.S. Kim, N.J. Yoo, S.H. Lee, Frameshift mutation of MARS gene encoding an aminoacyl-tRNA synthetase in gastric and colorectal carcinomas with microsatellite instability, *Gut Liver* 4 (2010) 430–431. PMC2956364.
- [37] Y.G. Ko, Y.S. Kang, E.K. Kim, S.G. Park, S. Kim, Nucleolar localization of human methionyl-tRNA synthetase and its role in ribosomal RNA synthesis, *J. Cell Biol.* 149 (2000) 567–574.
- [38] J.M. Lee, T. Kim, E.Y. Kim, A. Kim, D.K. Lee, N.H. Kwon, S. Kim, Y.S. Chang, Methionyl-tRNA synthetase is a useful diagnostic marker for lymph node metastasis in non-small cell lung cancer, *Yonsei Med. J.* 60 (2019) 1005–1012. PMC6813140.
- [39] T. Kim, K. Lee, J.H. Nahm, E.Y. Kim, S.H. Lee, Y.S. Chang, Methionyl-tRNA synthetase and aminoacyl-tRNA synthetases interacting multi-functional protein-lacking exon 2 as potential diagnostic biomarkers for lung cancer, *Am J Cancer Res* 11 (2021) 3135–3144. PMC8263685.
- [40] X. Zhang, J. Ling, G. Barcia, et al., Mutations in QARS, encoding glutamyl-tRNA synthetase, cause progressive microcephaly, cerebral-cerebellar atrophy, and intractable seizures, *Am. J. Hum. Genet.* 94 (2014) 547–558. PMC3980424.
- [41] Y. Yang-Hartwich, M.G. Soteras, Z.P. Lin, et al., p53 protein aggregation promotes platinum resistance in ovarian cancer, *Oncogene* 34 (2015) 3605–3616.

- [42] Y.G. Ko, E.Y. Kim, T. Kim, H. Park, H.S. Park, E.J. Choi, S. Kim, Glutamine-dependent antiapoptotic interaction of human glutamyl-tRNA synthetase with apoptosis signal-regulating kinase 1, *J. Biol. Chem.* 276 (2001) 6030–6036.
- [43] S.H. Shin, H.S. Kim, S.H. Jung, H.D. Xu, Y.B. Jeong, Y.J. Chung, Implication of leucyl-tRNA synthetase 1 (LARS1) over-expression in growth and migration of lung cancer cells detected by siRNA targeted knock-down analysis, *Exp. Mol. Med.* 40 (2008) 229–236. PMC2679304.
- [44] T. Tian, X. Li, J. Zhang, mTOR signaling in cancer and mTOR inhibitors in solid tumor targeting therapy, *Int. J. Mol. Sci.* 20 (2019). PMC6387042.
- [45] G.W. Vicary, J. Roman, Targeting the mammalian target of rapamycin in lung cancer, *Am. J. Med. Sci.* 352 (2016) 507–516. PMC5384343.
- [46] J.M. Han, S.J. Jeong, M.C. Park, G. Kim, N.H. Kwon, H.K. Kim, S.H. Ha, S.H. Ryu, S. Kim, Leucyl-tRNA synthetase is an intracellular leucine sensor for the mTORC1-signaling pathway, *Cell* 149 (2012) 410–424.
- [47] J.H. Kim, C. Lee, M. Lee, et al., Control of leucine-dependent mTORC1 pathway through chemical intervention of leucyl-tRNA synthetase and RagD interaction, *Nat. Commun.* 8 (2017) 732. PMC5622079.
- [48] M. Lee, J.H. Kim, I. Yoon, et al., Coordination of the leucine-sensing Rag GTPase cycle by leucyl-tRNA synthetase in the mTORC1 signaling pathway, *Proc. Natl. Acad. Sci. U. S. A.* 115 (2018) E5279–E5288.
- [49] Y. Guo, J. Tan, W. Xiong, S. Chen, L. Fan, Y. Li, Notch3 promotes 3T3-L1 pre-adipocytes differentiation by up-regulating the expression of LARS to activate the mTOR pathway, *J. Cell Mol Med* 24 (2020) 1116–1127. PMC6933334.
- [50] G. D'Hulst, I. Soro-Arnaiz, E. Masschelein, et al., PHD1 controls muscle mTORC1 in a hydroxylation-independent manner by stabilizing leucyl tRNA synthetase, *Nat. Commun.* 11 (2020) 174. PMC6954236.
- [51] R.J. Liu, T. Long, H. Li, J. Zhao, J. Li, M. Wang, A. Palencia, J. Lin, S. Cusack, E. D. Wang, Molecular basis of the multifaceted functions of human leucyl-tRNA synthetase in protein synthesis and beyond, *Nucleic Acids Res* 48 (2020) 4946–4959. PMC7229842.
- [52] S.A. McCune, H.P. Morris, G. Weber, Neoplastic transformation-linked alterations in arginyl-tRNA synthetase activity, *Biochim. Biophys. Acta* 561 (1979) 410–420.
- [53] A. Bottoni, D. Piccin, F. Tagliati, A. Luchin, M.C. Zatelli, E.C. degli Uberti, miR-15a and miR-16-1 down-regulation in pituitary adenomas, *J. Cell. Physiol.* 204 (2005) 280–285.
- [54] A. Bottoni, C. Vignali, D. Piccin, F. Tagliati, A. Luchin, M.C. Zatelli, E.C. Uberti, Proteasomes and RARS modulate AIMP1/EMAP II secretion in human cancer cell lines, *J. Cell. Physiol.* 212 (2007) 293–297.
- [55] Y. Fu, Y. Kim, K.S. Jin, et al., Structure of the ArgRS-GlnRS-AIMP1 complex and its implications for mammalian translation, *Proc. Natl. Acad. Sci. U. S. A.* 111 (2014) 15084–15089. PMC4210331.
- [56] G.T. Chung, R.W. Lung, A.B. Hui, et al., Identification of a recurrent transforming UBR5-ZNF423 fusion gene in EBV-associated nasopharyngeal carcinoma, *J. Pathol.* 231 (2013) 158–167. PMC4166696.
- [57] Q. Zhong, Z.H. Liu, Z.R. Lin, et al., The RARS-MAD1L1 fusion gene induces cancer stem cell-like properties and therapeutic resistance in nasopharyngeal carcinoma, *Clin. Cancer Res.* 24 (2018) 659–673. PMC5796860.
- [58] M. Jiao, H. Guo, Y. Chen, L. Li, L. Zhang, DARS-AS1 promotes clear cell renal cell carcinoma by sequestering miR-194-5p to up-regulate DARS, *Biomed. Pharmacother.* 128 (2020), 110323.
- [59] B. Dou, Z. Jiang, X. Chen, C. Wang, J. Wu, J. An, G. Sheng, Oncogenic long noncoding RNA DARS-AS1 in childhood acute myeloid leukemia by binding to microRNA-425, *Technol Cancer Res Treat* 19 (2020), 1533033820965580. PMC7592321.
- [60] Y. Chen, Q. Wu, J. Lin, J. Wei, DARS-AS1 accelerates the proliferation of cervical cancer cells via miR-628-5p/JAG1 axis to activate Notch pathway, *Cancer Cell Int* 20 (2020) 535. PMC7640441.
- [61] S.H. Chen, W. Yang, Y. Fan, G. Stocco, K.R. Crews, J.J. Yang, S.W. Paugh, C. H. Pui, W.E. Evans, M.V. Relling, A genome-wide approach identifies that the aspartate metabolism pathway contributes to asparaginase sensitivity, *Leukemia* 25 (2011) 66–74. PMC3097057.
- [62] B.H. Kim, W.Y. Jung, H. Lee, Y. Kang, Y.J. Jang, S.W. Hong, H.J. Jeong, S. O. Yoon, Lysyl-tRNA synthetase (KRS) expression in gastric carcinoma and tumor-associated inflammation, *Ann. Surg. Oncol.* 21 (2014) 2020–2027.
- [63] J.H. Suh, M.C. Park, P.C. Goughnour, et al., Plasma lysyl-tRNA synthetase 1 (KARS1) as a novel diagnostic and monitoring biomarker for colorectal cancer, *J Clin Med* 9 (2020). PMC7073917.
- [64] R. Zhang, L. Noordam, X. Ou, et al., The biological process of lysine-tRNA charging is therapeutically targetable in liver cancer, *Liver Int* 41 (2021) 206–219. PMC7820958.
- [65] S.H. Nam, D. Kim, M.S. Lee, et al., Noncanonical roles of membranous lysyl-tRNA synthetase in transducing cell-substrate signaling for invasive dissemination of colon cancer spheroids in 3D collagen I gels, *Oncotarget* 6 (2015) 21655–21674. PMC4673294.
- [66] H.J. Young, J.W. Lee, S. Kim, Function of membranous lysyl-tRNA synthetase and its implication for tumorigenesis, *Biochim. Biophys. Acta* 1864 (2016) 1707–1713.
- [67] S.H. Nam, M. Kang, J. Ryu, H.J. Kim, D. Kim, D.G. Kim, N.H. Kwon, S. Kim, J. W. Lee, Suppression of lysyl-tRNA synthetase, KRS, causes incomplete epithelial-mesenchymal transition and ineffective cell-extracellular matrix adhesion for migration, *Int. J. Oncol.* 48 (2016) 1553–1560.
- [68] D.G. Kim, J.W. Choi, J.Y. Lee, et al., Interaction of two translational components, lysyl-tRNA synthetase and p40/37LRP, in plasma membrane promotes laminin-dependent cell migration, *FASEB J* 26 (2012) 4142–4159.
- [69] S.B. Kim, H.R. Kim, M.C. Park, et al., Caspase-8 controls the secretion of inflammatory lysyl-tRNA synthetase in exosomes from cancer cells, *J. Cell Biol.* 216 (2017) 2201–2216. PMC5496609.
- [70] S.H. Nam, D. Kim, D. Lee, et al., Lysyl-tRNA synthetase-expressing colon spheroids induce M2 macrophage polarization to promote metastasis, *J. Clin. Invest.* 128 (2018) 5034–5055. PMC6205414.
- [71] S. Boulos, M.C. Park, M. Zeibak, et al., Serine 207 phosphorylated lysyl-tRNA synthetase predicts disease-free survival of non-small-cell lung carcinoma, *Oncotarget* 8 (2017) 65186–65198. PMC5630322.
- [72] A. Motzik, E. Amir, T. Erlich, et al., Post-translational modification of HINT1 mediates activation of MITF transcriptional activity in human melanoma cells, *Oncogene* 36 (2017) 4732–4738.
- [73] J. Wang, P. Fang, P. Schimmel, M. Guo, Side chain independent recognition of aminoacyl adenylates by the Hint1 transcription suppressor, *J Phys Chem B* 116 (2012) 6798–6805. PMC3375047.
- [74] R.J. Hause, A.L. Stark, N.N. Antao, et al., Identification and validation of genetic variants that influence transcription factor and cell signaling protein levels, *Am. J. Hum. Genet.* 95 (2014) 194–208. PMC4129400.
- [75] J. Liu, M. Zhu, W. Chen, et al., Genetic variants in multisynthetase complex genes are associated with DNA damage levels in Chinese populations, *Mutat. Res.* 786 (2016) 8–13.
- [76] Y.S. Lee, J.M. Han, T. Kang, Y.I. Park, H.M. Kim, S. Kim, Antitumor activity of the novel human cytokine AIMP1 in an in vivo tumor model, *Mol. Cells* 21 (2006) 213–217.
- [77] J.M. Han, H. Myung, S. Kim, Antitumor activity and pharmacokinetic properties of ARS-interacting multi-functional protein 1 (AIMP1/p43), *Cancer Lett* 287 (2010) 157–164.
- [78] S.S. Kim, S.Y. Hur, Y.R. Kim, N.J. Yoo, S.H. Lee, Expression of AIMP1, 2 and 3, the scaffolds for the multi-tRNA synthetase complex, is downregulated in gastric and colorectal cancer, *Tumori* 97 (2011) 380–385.
- [79] I.H. Bronkhorst, T.M. Jehs, E.M. Dijkgraaf, G.P. Luyten, P.A. van der Velden, S. H. van der Burg, M.J. Jager, Effect of hypoxic stress on migration and characteristics of monocytes in uveal melanoma, *JAMA Ophthalmol* 132 (2014) 614–621.
- [80] W. Cheng, X. Ren, C. Zhang, J. Cai, Y. Liu, S. Han, A. Wu, Bioinformatic profiling identifies an immune-related risk signature for glioblastoma, *Neurology* 86 (2016) 2226–2234.
- [81] Y. Tian, J. Wang, C. Qin, et al., Identifying 8-mRNAsi based signature for predicting survival in patients with head and neck squamous cell carcinoma via machine learning, *Front Genet* 11 (2020), 566159. PMC7721480.
- [82] W. Gao, C. An, X. Xue, et al., Mass spectrometric analysis identifies AIMP1 and LTA4H as FSCN1-binding proteins in laryngeal squamous cell carcinoma, *Proteomics* 19 (2019), e1900059.
- [83] L.A. Kolomiiets, N.V. Vorobyova, D.M. Lozhko, V.M. Zayets, A.I. Kornelyuk, Stabilization of AIMP1/p43 and EMAP II recombinant proteins in the complexes with polysaccharide dextran-70, *Pharmacol Rep* 72 (2020) 238–245.
- [84] H.J. Hong, H.X. Lim, J.H. Song, A. Lee, E. Kim, D. Cho, E.P. Cohen, T.S. Kim, Aminoacyl-tRNA synthetase-interacting multifunctional protein 1 suppresses tumor growth in breast cancer-bearing mice by negatively regulating myeloid-derived suppressor cell functions, *Cancer Immunol. Immunother.* 65 (2016) 61–72.
- [85] M.S. Kim, J.H. Song, E.P. Cohen, D. Cho, T.S. Kim, Aminoacyl tRNA synthetase-interacting multifunctional protein 1 activates nk cells via macrophages in vitro and in vivo, *J. Immunol.* 198 (2017) 4140–4147.
- [86] D. Liang, L. Tian, R. You, et al., AIMP1 potentiates TH1 polarization and is critical for effective antitumor and antiviral immunity, *Front. Immunol* 8 (2017) 1801. PMC5775236.
- [87] E. Kim, S.H. Kim, S. Kim, T.S. Kim, The novel cytokine p43 induces IL-12 production in macrophages via NF-κB activation, leading to enhanced IFN-γ production in CD4 T cells, *J. Immunol.* 176 (2006) 256–264.
- [88] B.C. Lee, I. O'Sullivan, E. Kim, S.G. Park, S.Y. Hwang, D. Cho, T.S. Kim, A DNA adjuvant encoding a fusion protein between anti-CD3 single-chain Fv and AIMP1 enhances T helper type 1 cell-mediated immune responses in antigen-sensitized mice, *Immunology* 126 (2009) 84–91. PMC2632698.
- [89] T.S. Kim, B.C. Lee, E. Kim, D. Cho, E.P. Cohen, Gene transfer of AIMP1 and B7.1 into epitope-loaded, fibroblasts induces tumor-specific CTL immunity, and prolongs the survival period of tumor-bearing mice, *Vaccine* 26 (2008) 5928–5934.
- [90] J.W. Choi, J.Y. Um, J.K. Kundu, Y.J. Surh, S. Kim, Multidirectional tumor-suppressive activity of AIMP2/p38 and the enhanced susceptibility of AIMP2 heterozygous mice to carcinogenesis, *Carcinogenesis* 30 (2009) 1638–1644.
- [91] J. Liu, H.J. Chung, M. Vogt, Y. Jin, D. Malide, L. He, M. Dunder, D. Levens, JTV1 co-activates FBP to induce USP29 transcription and stabilize p53 in response to oxidative stress, *EMBO J* 30 (2011) 846–858. PMC3049210.
- [92] J. Ma, M. Chen, S.K. Xia, et al., Prostaglandin E2 promotes liver cancer cell growth by the upregulation of FUSE-binding protein 1 expression, *Int. J. Oncol.* 42 (2013) 1093–1104.
- [93] D.G. Kim, J.Y. Lee, J.H. Lee, et al., Oncogenic mutation of AIMP2/p38 inhibits its tumor-suppressive interaction with Smurf2, *Cancer Res* 76 (2016) 3422–3436.
- [94] M.K. Yum, J.S. Kang, A.E. Lee, et al., AIMP2 controls intestinal stem cell compartments and tumorigenesis by modulating Wnt/β-catenin signaling, *Cancer Res* 76 (2016) 4559–4568.
- [95] K. Yin, Y. Zhang, S. Zhang, Y. Bao, J. Guo, G. Zhang, T. Li, Using weighted gene co-expression network analysis to identify key modules and hub genes in tongue squamous cell carcinoma, *Medicine (Baltimore)* 98 (2019) e17100. PMC6750333.

- [96] B.J. Park, Y.S. Oh, S.Y. Park, S.J. Choi, C. Rudolph, B. Schlegelberger, S. Kim, AIMP3 haploinsufficiency disrupts oncogene-induced p53 activation and genomic stability, *Cancer Res* 66 (2006) 6913–6918.
- [97] P.M. Gurung, A. Veerakumarasivam, M. Williamson, et al., Loss of expression of the tumour suppressor gene AIMP3 predicts survival following radiotherapy in muscle-invasive bladder cancer, *Int. J. Cancer* 136 (2015) 709–720.
- [98] D. Kim, S. Kim, Y. Oh, S. Park, Y. Jeon, H. Kim, H. Lee, S. Kim, AIMP3 deletion induces acute radiation syndrome-like phenotype in mice, *Sci. Rep.* 8 (2018) 15025. PMC6177475.
- [99] L. Ding, Y. Fang, Y. Li, Q. Hu, M. Ai, K. Deng, X. Huang, H. Xin, AIMP3 inhibits cell growth and metastasis of lung adenocarcinoma through activating a miR-96-5p-AIMP3-p53 axis, *J Cell Mol Med* 25 (2021) 3019–3030. PMC7957209.
- [100] S.M. Kim, Y. Jeon, D. Kim, H. Jang, J.S. Bae, M.K. Park, H. Kim, S. Kim, H. Lee, AIMP3 depletion causes genome instability and loss of stemness in mouse embryonic stem cells, *Cell Death Dis* 9 (2018) 972. PMC6155375.
- [101] J. Kao, J. Ryan, G. Brett, et al., Endothelial monocyte-activating polypeptide II. A novel tumor-derived polypeptide that activates host-response mechanisms, *J. Biol. Chem.* 267 (1992) 20239–20247.
- [102] J. Kao, K. Houck, Y. Fan, et al., Characterization of a novel tumor-derived cytokine. Endothelial-monocyte activating polypeptide II, *J. Biol. Chem.* 269 (1994) 25106–25119.
- [103] P.C. Wu, H.R. Alexander, J. Huang, P. Hwu, M. Gnant, A.C. Berger, E. Turner, O. Wilson, S.K. Libutti, In vivo sensitivity of human melanoma to tumor necrosis factor (TNF)-alpha is determined by tumor production of the novel cytokine endothelial-monocyte activating polypeptide II (EMAPII), *Cancer Res* 59 (1999) 205–212.
- [104] M.F. Gnant, A.C. Berger, J. Huang, M. Puhlmann, P.C. Wu, M.J. Merino, D. L. Bartlett, H.R. Alexander Jr., S.K. Libutti, Sensitization of tumor necrosis factor alpha-resistant human melanoma by tumor-specific in vivo transfer of the gene encoding endothelial monocyte-activating polypeptide II using recombinant vaccinia virus, *Cancer Res* 59 (1999) 4668–4674.
- [105] T.E. Lans, T.L. ten Hagen, R. van Horsen, P.C. Wu, S.T. van Tiel, S.K. Libutti, H. R. Alexander, A.M. Eggermont, Improved antitumor response to isolated limb perfusion with tumor necrosis factor after upregulation of endothelial monocyte-activating polypeptide II in soft tissue sarcoma, *Ann. Surg. Oncol.* 9 (2002) 812–819.
- [106] G. Barnett, A.M. Jakobsen, M. Tas, K. Rice, J. Carmichael, J.C. Murray, Prostate adenocarcinoma cells release the novel proinflammatory polypeptide EMAP-II in response to stress, *Cancer Res* 60 (2000) 2850–2857.
- [107] A.C. Berger, H.R. Alexander, G. Tang, et al., Endothelial monocyte activating polypeptide II induces endothelial cell apoptosis and may inhibit tumor angiogenesis, *Microvasc. Res.* 60 (2000) 70–80.
- [108] A.T. Tandle, M. Calvani, B. Uranchimeg, D. Zahavi, G. Melillo, S.K. Libutti, Endothelial monocyte activating polypeptide-II modulates endothelial cell responses by degrading hypoxia-inducible factor-1alpha through interaction with PSMa7, a component of the proteasome, *Exp. Cell Res.* 315 (2009) 1850–1859.
- [109] A. Ferrario, K.F. von Tiehl, N. Rucker, M.A. Schwarz, P.S. Gill, C.J. Gomer, Antiangiogenic treatment enhances photodynamic therapy responsiveness in a mouse mammary carcinoma, *Cancer Res* 60 (2000) 4066–4069.
- [110] M. Yamamoto, T. Fukushima, Y. Ueno, S. Hayashi, H. Kimura, G. Soma, M. Tomonaga, Clinical significance of the expression of endothelial-monocyte activating polypeptide II (EMAPII) in the treatment of glioblastoma with recombinant mutant human tumor necrosis factor-alpha (TNF-SAM2), *Anticancer Res* 20 (2000) 4081–4086.
- [111] H.J. Kim, R. Lotan, Identification of retinoid-modulated proteins in squamous carcinoma cells using high-throughput immunoblotting, *Cancer Res* 64 (2004) 2439–2448.
- [112] R.E. Schwarz, M.A. Schwarz, In vivo therapy of local tumor progression by targeting vascular endothelium with EMAP-II, *J. Surg. Res.* 120 (2004) 64–72.
- [113] A.T. Tandle, C. Mazzanti, H.R. Alexander, D.D. Roberts, S.K. Libutti, Endothelial monocyte activating polypeptide-II induced gene expression changes in endothelial cells, *Cytokine* 30 (2005) 347–358.
- [114] Z. Li, Y.H. Liu, Y.X. Xue, H. Xie, L.B. Liu, Role of ATP synthase alpha subunit in low-dose endothelial monocyte-activating polypeptide-II-induced opening of the blood-tumor barrier, *J. Neurol. Sci.* 300 (2011) 52–58.
- [115] Z. Li, Y.H. Liu, Y.X. Xue, L.B. Liu, H. Xie, Mechanisms for endothelial monocyte-activating polypeptide-II-induced opening of the blood-tumor barrier, *J. Mol. Neurosci.* 47 (2012) 408–417.
- [116] J. Liu, L. Liu, Y. Xue, F. Meng, S. Li, P. Wang, Y. Liu, Anti-neoplastic activity of low-dose endothelial-monocyte activating polypeptide-II results from defective autophagy and G2/M arrest mediated by PI3K/Akt/FoxO1 axis in human glioblastoma stem cells, *Biochem. Pharmacol.* 89 (2014) 477–489.
- [117] Q. Yu, L. Liu, P. Wang, Y. Yao, Y. Xue, Y. Liu, EMAP-II sensitize U87MG and glioma stem-like cells to temozolomide via induction of autophagy-mediated cell death and G2/M arrest, *Cell Cycle* 16 (2017) 1085–1092. PMC5499844.
- [118] W. Zhou, L. Liu, Y. Xue, J. Zheng, X. Liu, J. Ma, Z. Li, Y. Liu, Combination of endothelial-monocyte-activating polypeptide-II with temozolomide suppress malignant biological behaviors of human glioblastoma stem cells via miR-590-3p/MACC1 inhibiting PI3K/AKT/mTOR signal pathway, *Front Mol Neurosci* 10 (2017) 68. PMC5346543.
- [119] R. Clarijs, L. Schalkwijk, D.J. Ruiters, R.M. de Waal, EMAP-II expression is associated with macrophage accumulation in primary uveal melanoma, *Invest. Ophthalmol. Vis. Sci.* 44 (2003) 1801–1806.
- [120] J.C. Murray, P. Symonds, W. Ward, M. Huggins, A. Tiga, K. Rice, Y.M. Heng, I. Todd, R.A. Robins, Colorectal cancer cells induce lymphocyte apoptosis by an endothelial monocyte-activating polypeptide-II-dependent mechanism, *J. Immunol.* 172 (2004) 274–281.
- [121] W. Faisal, P. Symonds, S. Panjwani, Y. Heng, J.C. Murray, Cell-surface associated p43/endothelial-monocyte-activating-polypeptide-II in hepatocellular carcinoma cells induces apoptosis in T-lymphocytes, *Asian J Surg* 30 (2007) 13–22.
- [122] J.C. Murray, Y.M. Heng, P. Symonds, K. Rice, W. Ward, M. Huggins, I. Todd, R. A. Robins, Endothelial monocyte-activating polypeptide-II (EMAP-II): a novel inducer of lymphocyte apoptosis, *J. Leukoc. Biol.* 75 (2004) 772–776.
- [123] M.M. Youssef, P. Symonds, I.O. Ellis, J.C. Murray, EMAP-II-dependent lymphocyte killing is associated with hypoxia in colorectal cancer, *Br. J. Cancer* 95 (2006) 735–743. PMC2360520.
- [124] Y.G. Ko, H. Park, T. Kim, et al., A cofactor of tRNA synthetase, p43, is secreted to up-regulate proinflammatory genes, *J. Biol. Chem.* 276 (2001) 23028–23033.
- [125] U.E. Knies, H.A. Behrens, C.A. Mitchell, U. Deutsch, W. Risau, H.C. Drexler, M. Claus, Regulation of endothelial monocyte-activating polypeptide II release by apoptosis, *Proc. Natl. Acad. Sci. U. S. A.* 95 (1998) 12322–12327. PMC22830.
- [126] J.W. Choi, D.G. Kim, A.E. Lee, et al., Cancer-associated splicing variant of tumor suppressor AIMP2/p38: pathological implication in tumorigenesis, *PLoS Genet* 7 (2011), e1001351. PMC3069106.
- [127] Q. Cao, J. Zhang, T. Zhang, AIMP2-DX2 promotes the proliferation, migration, and invasion of nasopharyngeal carcinoma cells, *Biomed Res Int* 2018 (2018), 9253036. PMC5941793.
- [128] J.Y. Jung, E.Y. Kim, A. Kim, et al., Ratio of autoantibodies of tumor suppressor AIMP2 and its oncogenic variant is associated with clinical outcome in lung cancer, *J Cancer* 8 (2017) 1347–1354. PMC5479239.
- [129] J.W. Choi, J.W. Lee, J.K. Kim, et al., Splicing variant of AIMP2 as an effective target against chemoresistant ovarian cancer, *J Mol Cell Biol* 4 (2012) 164–173.
- [130] S.H. Chang, Y.S. Chung, S.K. Hwang, J.T. Kwon, A. Minaei-Tehrani, S. Kim, S. B. Park, Y.S. Kim, M.H. Cho, Lentiviral vector-mediated shRNA against AIMP2-DX2 suppresses lung cancer cell growth through blocking glucose uptake, *Mol. Cells* 33 (2012) 553–562. PMC3887752.
- [131] J. Ku, R. Kim, D. Kim, et al., Single-cell analysis of AIMP2 splice variants informs on drug sensitivity and prognosis in hematologic cancer, *Commun Biol* 3 (2020) 630. PMC7599330.
- [132] S. Lim, H.Y. Cho, D.G. Kim, et al., Targeting the interaction of AIMP2-DX2 with HSP70 suppresses cancer development, *Nat. Chem. Biol.* 16 (2020) 31–41.
- [133] Y.S. Won, S.W. Lee, Selective regression of cancer cells expressing a splicing variant of AIMP2 through targeted RNA replacement by trans-splicing ribozyme, *J. Biotechnol.* 158 (2012) 44–49.
- [134] S.K. Hwang, S.H. Chang, A. Minaei-Tehrani, Y.S. Kim, M.H. Cho, Lentivirus-AIMP2-DX2 shRNA suppresses cell proliferation by regulating Akt1 signaling pathway in the lungs of AIMP2(+/-) mice, *J Aerosol Med Pulm Drug Deliv* 26 (2013) 165–173.
- [135] K. Kim, S.J. Park, S. Na, J.S. Kim, H. Choi, Y.K. Kim, E. Paek, C. Lee, Reinvestigation of aminoacyl-tRNA synthetase core complex by affinity purification-mass spectrometry reveals TARSL2 as a potential member of the complex, *PLoS ONE* (8) (2013) e81734. PMC3846882.
- [136] X.L. Zhou, Y. Chen, Q.Y. Zeng, Z.R. Ruan, P. Fang, E.D. Wang, Newly acquired N-terminal extension targets threonyl-tRNA synthetase-like protein into the multiple tRNA synthetase complex, *Nucleic Acids Res* 47 (2019) 8662–8674. PMC6794377.
- [137] Y. Zhang, F. Chen, L.A. Donehower, M.E. Scheurer, C.J. Creighton, A pediatric brain tumor atlas of genes deregulated by somatic genomic rearrangement, *Nat. Commun.* 12 (2021) 937. PMC7876141.
- [138] F.C. von Rundstedt, K. Rajapakse, J. Ma, et al., Integrative pathway analysis of metabolic signature in bladder cancer: a linkage to the cancer genome atlas project and prediction of survival, *J. Urol.* 195 (2016) 1911–1919. PMC4861129.
- [139] M. Miranda, D. Le Corre, J.P. Waller, A complex from cultured Chinese hamster ovary cells containing nine aminoacyl-tRNA synthetases. Thermolabile leucyl-tRNA synthetase from the tsH1 mutant cell line is an integral component of this complex, *Eur. J. Biochem.* 147 (1985) 281–289.
- [140] P. Kerjan, C. Cerini, M. Sémériva, M. Miranda, The multienzyme complex containing nine aminoacyl-tRNA synthetases is ubiquitous from *Drosophila* to mammals, *Biochim. Biophys. Acta* 1199 (1994) 293–297.
- [141] J.M. Han, M.J. Lee, S.G. Park, S.H. Lee, E. Razin, E.C. Choi, S. Kim, Hierarchical network between the components of the multi-tRNA synthetase complex: implications for complex formation, *J. Biol. Chem.* 281 (2006) 38663–38667.
- [142] M.P. Deutscher, The eucaryotic aminoacyl-tRNA synthetase complex: suggestions for its structure and function, *J. Cell Biol.* 99 (1984) 373–377. PMC2113280.
- [143] S.W. Lee, B.H. Cho, S.G. Park, S. Kim, Aminoacyl-tRNA synthetase complexes: beyond translation, *J. Cell Sci.* 117 (2004) 3725–3734.
- [144] E.V. Smirnova, V.A. Lakunina, I. Tarassov, I.A. Krashennnikov, P.A. Kamenski, Noncanonical functions of aminoacyl-tRNA synthetases, *Biochemistry (Mosc)* 77 (2012) 15–25.
- [145] M. Guo, P. Schimmel, Essential nontranslational functions of tRNA synthetases, *Nat. Chem. Biol.* 9 (2013) 145–153.
- [146] D. Blocquel, L. Sun, Z. Matuszek, et al., CMT disease severity correlates with mutation-induced open conformation of histidyl-tRNA synthetase, not aminoacylation loss, in patient cells, *Proc. Natl. Acad. Sci. U. S. A.* 116 (2019) 19440–19448. PMC6765236.
- [147] S. Cho, S.B. Kim, Y. Lee, et al., Endogenous TLR2 ligand embedded in the catalytic region of human cysteinyl-tRNA synthetase 1, *J Immunother Cancer* 8 (2020). PMC7254149.
- [148] K. Wakasugi, P. Schimmel, Two distinct cytokines released from a human aminoacyl-tRNA synthetase, *Science* 284 (1999) 147–151.

- [149] C. Zhang, X. Lin, Q. Zhao, Y. Wang, F. Jiang, C. Ji, Y. Li, J. Gao, J. Li, L. Shen, YARS as an oncogenic protein that promotes gastric cancer progression through activating PI3K-Akt signaling, *J. Cancer Res. Clin. Oncol.* 146 (2020) 329–342. PMC6985085.
- [150] M. Jin, Unique roles of tryptophanyl-tRNA synthetase in immune control and its therapeutic implications, *Exp. Mol. Med.* 51 (2019) 1–10. PMC6321835.
- [151] A. Ghanipour, K. Jirstrom, F. Ponten, B. Glimelius, L. Pahlman, H. Birgisson, The prognostic significance of tryptophanyl-tRNA synthetase in colorectal cancer, *Cancer Epidemiol. Biomarkers Prev.* 18 (2009) 2949–2956.
- [152] M.C. Park, T. Kang, D. Jin, et al., Secreted human glycyl-tRNA synthetase implicated in defense against ERK-activated tumorigenesis, *Proc. Natl. Acad. Sci. U. S. A.* 109 (2012) E640–E647, 3306665.
- [153] J. Zhao, H. Bai, X. Li, et al., Glucose-sensitive acetylation of Seryl tRNA synthetase regulates lipid synthesis in breast cancer, *Signal Transduct Target Ther* 6 (2021) 303. PMC8368063.
- [154] A. Arif, J. Jia, R. Mukhopadhyay, B. Willard, M. Kinter, P.L. Fox, Two-site phosphorylation of EPRS coordinates multimodal regulation of noncanonical translational control activity, *Mol. Cell* 35 (2009) 164–180. PMC3002251.
- [155] M. Oner, E. Lin, M.C. Chen, et al., Future aspects of CDK5 in prostate cancer: from pathogenesis to therapeutic implications, *Int. J. Mol. Sci* 20 (2019). PMC6720211.
- [156] D.M. Maruani, T.N. Spiegel, E.N. Harris, A.S. Shachter, H.A. Unger, S. Herrero-Gonzalez, M.K. Holz, Estrogenic regulation of S6K1 expression creates a positive regulatory loop in control of breast cancer cell proliferation, *Oncogene* 31 (2012) 5073–5080. PMC3342462.
- [157] A. Arif, F. Terenzi, A.A. Potdar, et al., EPRS is a critical mTORC1-S6K1 effector that influences adiposity in mice, *Nature* 542 (2017) 357–361. PMC5480610.
- [158] E.Y. Lee, H.C. Lee, H.K. Kim, et al., Infection-specific phosphorylation of glutamyl-prolyl tRNA synthetase induces antiviral immunity, *Nat. Immunol.* 17 (2016) 1252–1262. PMC5173487.
- [159] N.H. Kwon, T. Kang, J.Y. Lee, et al., Dual role of methionyl-tRNA synthetase in the regulation of translation and tumor suppressor activity of aminoacyl-tRNA synthetase-interacting multifunctional protein-3, *Proc. Natl. Acad. Sci. U. S. A.* 108 (2011) 19635–19640. PMC3241768.
- [160] J.Y. Lee, D.G. Kim, B.G. Kim, et al., Promiscuous methionyl-tRNA synthetase mediates adaptive mistranslation to protect cells against oxidative stress, *J. Cell Sci.* 127 (2014) 4234–4245. PMC4179492.
- [161] J.V. Olsen, M. Vermeulen, A. Santamaria, et al., Quantitative phosphoproteomics reveals widespread full phosphorylation site occupancy during mitosis, *Sci. Signal.* 3 (2010) ra3.
- [162] K.R. Kim, S.H. Park, H.S. Kim, K.H. Rhee, B.G. Kim, D.G. Kim, M.S. Park, H. J. Kim, S. Kim, B.W. Han, Crystal structure of human cytosolic aspartyl-tRNA synthetase, a component of multi-tRNA synthetase complex, *Proteins* 81 (2013) 1840–1846. PMC3824080.
- [163] Y. Ofir-Birin, P. Fang, S.P. Bennett, et al., Structural switch of lysyl-tRNA synthetase between translation and transcription, *Mol. Cell* 49 (2013) 30–42.
- [164] C.R. Goding, H. Arneither, MITF—the first 25 years, *Genes Dev* 33 (2019) 983–1007. PMC6672050.
- [165] J.M. Han, B.J. Park, S.G. Park, Y.S. Oh, S.J. Choi, S.W. Lee, S.K. Hwang, S. H. Chang, M.H. Cho, S. Kim, AIMP2/p38, the scaffold for the multi-tRNA synthetase complex, responds to genotoxic stresses via p53, *Proc. Natl. Acad. Sci. U. S. A.* 105 (2008) 11206–11211.
- [166] H.Y. Lei, X.L. Zhou, Z.R. Ruan, W.C. Sun, G. Eriani, E.D. Wang, Calpain cleaves most components in the multiple aminoacyl-tRNA synthetase complex and affects their functions, *J. Biol. Chem.* 290 (2015) 26314–26327. PMC4646279.
- [167] V. Shalakh, M. Kaminska, R. Mitnacht-Kraus, P. Vandenabeele, M. Claus, M. Mirande, The EMAPII cytokine is released from the mammalian multisynthetase complex after cleavage of its p43/proEMAPII component, *J. Biol. Chem.* 276 (2001) 23769–23776.
- [168] V. Shalakh, L. Guigou, M. Kaminska, M.P. Wautier, J.L. Wautier, M. Mirande, Characterization of p43(ARF), a derivative of the p43 component of multi-aminoacyl-tRNA synthetase complex released during apoptosis, *J. Biol. Chem.* 282 (2007) 10935–10943.
- [169] D. Halawani, V. Gogonea, J.A. DiDonato, et al., Structural control of caspase-generated glutamyl-tRNA synthetase by appended noncatalytic WHEP domains, *J. Biol. Chem.* 293 (2018) 8843–8860. PMC5995526.
- [170] M.I. Mendes, M. Gutierrez Salazar, K. Guerrero, et al., Bi-allelic mutations in EPRS, encoding the glutamyl-prolyl-aminoacyl-tRNA synthetase, cause a hypomyelinating leukodystrophy, *Am. J. Hum. Genet.* 102 (2018) 676–684. PMC5985283.
- [171] K. Hirata, N. Okamoto, C. Ichikawa, S. Inoue, M. Nozaki, K. Banno, T. Takenouchi, H. Suzuki, K. Kosaki, Severe course with lethal hepatocellular injury and skeletal muscular dysgenesis in a neonate with infantile liver failure syndrome type 1 caused by novel LARS1 mutations, *Am. J. Med. Genet. A* 185 (2021) 866–870.
- [172] R.J. Taft, A. Vanderver, R.J. Leventer, et al., Mutations in DARS cause hypomyelination with brain stem and spinal cord involvement and leg spasticity, *Am. J. Hum. Genet.* 92 (2013) 774–780. PMC3644624.
- [173] R. Kopajtich, K. Murayama, A.R. Janecke, et al., Biallelic IARS mutations cause growth retardation with prenatal onset, intellectual disability, muscular hypotonia, and infantile hepatopathy, *Am. J. Hum. Genet.* 99 (2016) 414–422. PMC4974065.
- [174] M. Nafisinia, N. Sobreira, L. Riley, W. Gold, B. Uhlenberg, C. Weiss, C. Boehm, K. Prelog, R. Ouvrier, J. Christodoulou, Mutations in RARS cause a hypomyelination disorder akin to Pelizaeus-Merzbacher disease, *Eur. J. Hum. Genet.* 25 (2017) 1134–1141. PMC5602020.
- [175] S. Scheidecker, S. Bar, C. Stoetzel, et al., Mutations in KARS cause a severe neurological and neurosensory disease with optic neuropathy, *Hum. Mutat.* 40 (2019) 1826–1840.
- [176] S.-J. Lin, B. Vona, P.G. Barbalho, et al., Biallelic variants in KARS1 are associated with neurodevelopmental disorders and hearing loss recapitulated by the knockout zebrafish, *Genet Med* 23 (2021) 1933–1943.
- [177] Z. Iqbal, L. Puttmann, L. Musante, et al., Missense variants in AIMP1 gene are implicated in autosomal recessive intellectual disability without neurodegeneration, *Eur. J. Hum. Genet.* 24 (2016) 392–399. PMC4755381.
- [178] A. Shukla, A. Das Bhowmik, M. Hebbar, K.V. Rajagopal, K.M. Girisha, N. Gupta, A. Dalal, Homozygosity for a nonsense variant in AIMP2 is associated with a progressive neurodevelopmental disorder with microcephaly, seizures, and spastic quadriplegia, *J. Hum. Genet.* 63 (2018) 19–25.
- [179] K.J. Kim, M.C. Park, S.J. Choi, et al., Determination of three-dimensional structure and residues of the novel tumor suppressor AIMP3/p18 required for the interaction with ATM, *J. Biol. Chem.* 283 (2008) 14032–14040.
- [180] Z. Hei, S. Wu, Z. Liu, J. Wang, P. Fang, Retractile lysyl-tRNA synthetase-AIMP2 assembly in the human multi-aminoacyl-tRNA synthetase complex, *J. Biol. Chem.* 294 (2019) 4775–4783. PMC6442029.
- [181] S.I. Grivennikov, F.R. Greten, M. Karin, Immunity, inflammation, and cancer, *Cell* 140 (2010) 883–899. PMC2866629.
- [182] G. Multhoff, M. Molls, J. Radons, Chronic inflammation in cancer development, *Front. Immunol.* 2 (2011) 98. PMC3342348.
- [183] J. Condeelis, J.W. Pollard, Macrophages: obligate partners for tumor cell migration, invasion, and metastasis, *Cell* 124 (2006) 263–266.
- [184] A. Nie, B. Sun, Z. Fu, D. Yu, Roles of aminoacyl-tRNA synthetases in immune regulation and immune diseases, *Cell Death Dis* 10 (2019) 901. PMC6883034.
- [185] S.G. Park, H.J. Kim, Y.H. Min, E.C. Choi, Y.K. Shin, B.J. Park, S.W. Lee, S. Kim, Human lysyl-tRNA synthetase is secreted to trigger proinflammatory response, *Proc. Natl. Acad. Sci. U. S. A.* 102 (2005) 6356–6361.
- [186] H.S. Kwon, M.C. Park, D.G. Kim, K. Cho, Y.W. Park, J.M. Han, S. Kim, Identification of CD23 as a functional receptor for the proinflammatory cytokine AIMP1/p43, *J. Cell Sci.* 125 (2012) 4620–4629.
- [187] D.D. Lee, C.V. Lal, E.A. Persad, C.W. Lowe, A.M. Schwarz, N. Awasthi, R. E. Schwarz, M.A. Schwarz, Endothelial monocyte-activating polypeptide ii mediates macrophage migration in the development of hyperoxia-induced lung disease of prematurity, *Am. J. Respir. Cell Mol. Biol.* 55 (2016) 602–612. PMC5070113.
- [188] D.I. Kotov, J.S. Mitchell, T. Pengo, C. Ruedl, S.S. Way, R.A. Langlois, B.T. Fife, M. K. Jenkins, TCR affinity biases Th cell differentiation by regulating CD25, Eef1e1, and Gbp2, *J. Immunol.* 202 (2019) 2535–2545. PMC6478541.
- [189] D.G. Song, D. Kim, J.W. Jung, S.H. Nam, J.E. Kim, H.J. Kim, C.H. Pan, S. Kim, J.W. Lee, Glutamyl-prolyl-tRNA synthetase regulates epithelial expression of mesenchymal markers and extracellular matrix proteins: implications for idiopathic pulmonary fibrosis, *Front. Pharmacol.* 9 (2018) 1337. PMC6256097.
- [190] H. Qin, L. Wang, T. Feng, et al., TGF-beta promotes Th17 cell development through inhibition of SOCS3, *J. Immunol.* 183 (2009) 97–105. PMC2851540.
- [191] S.R. Bailey, M.H. Nelson, R.A. Himes, Z. Li, S. Mehrotra, C.M. Paulos, Th17 cells in cancer: the ultimate identity crisis, *Front. Immunol.* 5 (2014) 276. PMC4060300.
- [192] M.S. Sundrud, S.B. Koralov, M. Feuerer, et al., Halofuginone inhibits Th17 cell differentiation by activating the amino acid starvation response, *Science* 324 (2009) 1334–1338. PMC2803727.
- [193] Y.S. Suh, E. Yeom, J.W. Nam, K.J. Min, J. Lee, K. Yu, Methionyl-tRNA synthetase regulates lifespan in *Drosophila*, *Mol. Cells* 43 (2020) 304–311. PMC7103878.
- [194] A. Fagbemi, W.G. Newman, S.G. Tangye, S.M. Hughes, E. Cheesman, P. D. Arkwright, Refractory very early-onset inflammatory bowel disease associated with cytosolic isoleucyl-tRNA synthetase deficiency: a case report, *World J. Gastroenterol.* 26 (2020) 1841–1846. PMC7183863.
- [195] T.L. Keller, D. Zocco, M.S. Sundrud, et al., Halofuginone and other febrifugine derivatives inhibit prolyl-tRNA synthetase, *Nat. Chem. Biol.* 8 (2012) 311–317. PMC3281520.
- [196] P. Juarez, P.G.J. Fournier, K.S. Mohammad, R.C. McKenna, H.W. Davis, X. H. Peng, M. Niewolna, A. Mauviel, J.M. Chirgwin, T.A. Guise, Halofuginone inhibits TGF-beta/BMP signaling and in combination with zoledronic acid enhances inhibition of breast cancer bone metastasis, *Oncotarget* 8 (2017) 86447–86462. PMC5689697.
- [197] K. Tsuchida, T. Tsujita, M. Hayashi, et al., Halofuginone enhances the chemosensitivity of cancer cells by suppressing NRF2 accumulation, *Free Radic. Biol. Med.* 103 (2017) 236–247.
- [198] T.L. McGaha, R.G. Phelps, H. Speria, C. Bona, Halofuginone, an inhibitor of type-I collagen synthesis and skin sclerosis, blocks transforming-growth-factor-beta-mediated Smad3 activation in fibroblasts, *J. Invest. Dermatol.* 118 (2002) 461–470.
- [199] C. Follo, C. Vidoni, F. Morani, A. Ferraresi, C. Seca, C. Isidoro, Amino acid response by halofuginone in cancer cells triggers autophagy through proteasome degradation of mTOR, *Cell Commun Signal* 17 (2019) 39. PMC6498594.
- [200] M. Pines, Halofuginone for fibrosis, regeneration and cancer in the gastrointestinal tract, *World J. Gastroenterol.* 20 (2014) 14778–14786. PMC4209542.
- [201] H. Bharathkumar, C.D. Mohan, S. Rangappa, et al., Screening of quinoline, 1,3-benzoxazine, and 1,3-oxazine-based small molecules against isolated methionyl-tRNA synthetase and A549 and HCT116 cancer cells including an in silico binding mode analysis, *Org. Biomol. Chem.* 13 (2015) 9381–9387.
- [202] G. Gao, Y. Yao, K. Li, et al., A human leucyl-tRNA synthetase as an anticancer target, *Onco. Targets Ther.* 8 (2015) 2933–2942. PMC4610879.

- [203] E.Y. Kim, J.G. Lee, J.M. Lee, et al., Therapeutic effects of the novel Leucyl-tRNA synthetase inhibitor BC-LI-0186 in non-small cell lung cancer, *Ther Adv Med Oncol* 11 (2019), 1758835919846798. PMC6535710.
- [204] Y. Iiboshi, P.J. Papst, H. Kawasome, H. Hosoi, R.T. Abraham, P.J. Houghton, N. Terada, Amino acid-dependent control of p70(s6k). Involvement of tRNA aminoacylation in the regulation, *J. Biol. Chem.* 274 (1999) 1092–1099.
- [205] S. Yoon, J.H. Kim, I. Yoon, C. Kim, S.E. Kim, Y. Koh, S.J. Jeong, J. Lee, S. Kim, J. Lee, Discovery of (S)-4-isobutyloxazolidin-2-one as a novel leucyl-tRNA synthetase (LRS)-targeted mTORC1 inhibitor, *Bioorg. Med. Chem. Lett.* 26 (2016) 3038–3041.
- [206] S. Yoon, J.H. Kim, S.E. Kim, et al., Discovery of leucyladenylate sulfamates as novel leucyl-tRNA synthetase (LRS)-targeted mammalian target of rapamycin complex 1 (mTORC1) inhibitors, *J. Med. Chem.* 59 (2016) 10322–10328.
- [207] S. Yoon, J.H. Kim, Y. Koh, et al., Discovery of simplified leucyladenylate sulfamates as novel leucyl-tRNA synthetase (LRS)-targeted mammalian target of rapamycin complex 1 (mTORC1) inhibitors, *Bioorg. Med. Chem.* 25 (2017) 4145–4152.
- [208] S. Yoon, D. Zuo, J.H. Kim, et al., Discovery of novel leucyladenylate sulfamate surrogates as leucyl-tRNA synthetase (LRS)-targeted mammalian target of rapamycin complex 1 (mTORC1) inhibitors, *Bioorg. Med. Chem.* 26 (2018) 4073–4079.
- [209] S. Yoon, S.E. Kim, J.H. Kim, et al., Structure-activity relationship of leucyladenylate sulfamate analogues as leucyl-tRNA synthetase (LRS)-targeting inhibitors of Mammalian target of rapamycin complex 1 (mTORC1), *Bioorg. Med. Chem.* 27 (2019) 1099–1109.
- [210] S. Lee, N.H. Kwon, B. Seo, et al., Discovery of novel potent migrastatic thiazolo [5,4-b]pyridines targeting lysyl-tRNA synthetase (KRS) for treatment of cancer metastasis, *Eur. J. Med. Chem.* 218 (2021), 113405.
- [211] D.G. Kim, J.Y. Lee, N.H. Kwon, et al., Chemical inhibition of prometastatic lysyl-tRNA synthetase-laminin receptor interaction, *Nat. Chem. Biol.* 10 (2014) 29–34. PMC4021855.
- [212] A.K. Bence, P.A. Crooks, The mechanism of l-canavanine cytotoxicity: arginyl tRNA synthetase as a novel target for anticancer drug discovery, *J. Enzyme Inhib Med Chem* 18 (2003) 383–394.
- [213] H.S. Lee, D.G. Kim, Y.S. Oh, et al., Chemical suppression of an oncogenic splicing variant of AIMP2 induces tumour regression, *Biochem. J.* 454 (2013) 411–416.
- [214] A.Y. Oh, Y.S. Jung, J. Kim, et al., Inhibiting DX2-p14/ARF interaction exerts antitumor effects in lung cancer and delays tumor progression, *Cancer Res* 76 (2016) 4791–4804.
- [215] A. Sivaraman, D.G. Kim, D. Bhattarai, et al., Synthesis and structure-activity relationships of arylsulfonamides as AIMP2-DX2 inhibitors for the development of a novel anticancer therapy, *J. Med. Chem.* 63 (2020) 5139–5158.
- [216] D.G. Kim, C.M. Park, S. Huddar, S. Lim, S. Kim, S. Lee, Anticancer activity of pyrimethamine via ubiquitin mediated degradation of AIMP2-DX2, *Molecules* 25 (2020). PMC7355952.